

SHORT ANTIBIOTIC COURSES IN TRANSURETHRAL PROSTATIC RESECTION

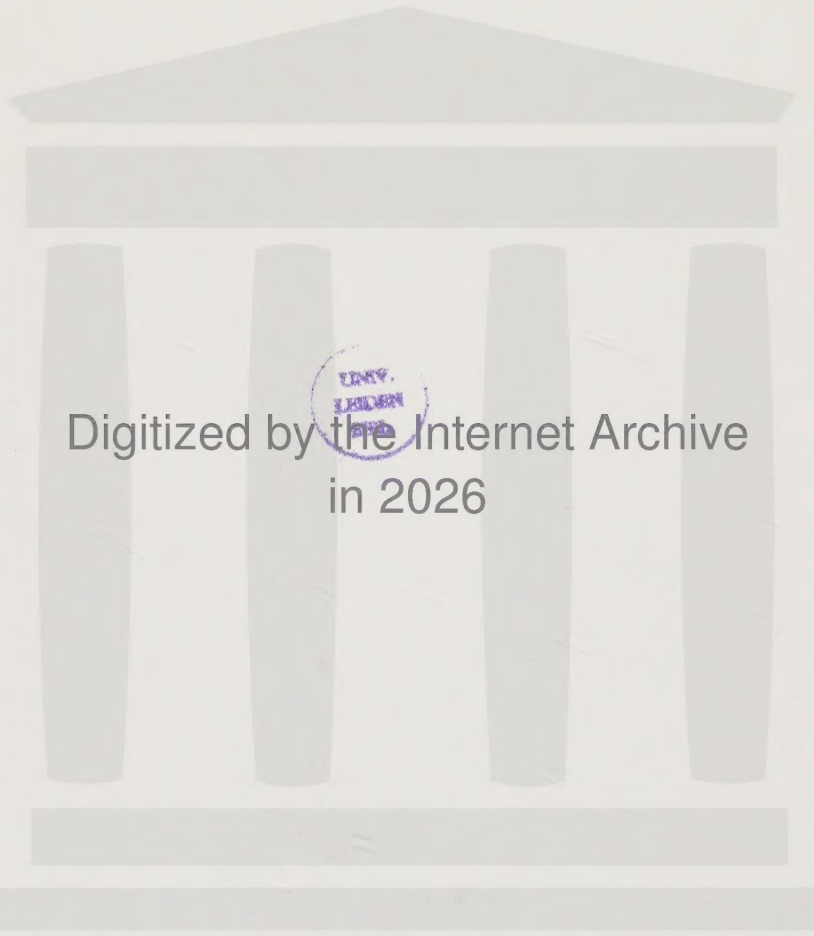
Magnus Grabe



LUND

~~Malmö~~ 1984

Distributed by Almquist & Wiksell



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41546724_0060

SHORT ANTIBIOTIC COURSES IN TRANSURETHRAL
PROSTATIC RESECTION

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten
vid Universitetet i Lund för avläggande av doktorsexamen
i medicinsk vetenskap kommer att offentligen försvaras
i Medicinklinikens Aula, Malmö Allmänna Sjukhus,
fredagen den 17 februari 1984 kl. 09.15.

av

Magnus Grabe
leg läk, M1m

Organization LUND UNIVERSITY Departments of Urology and Medical Microbiology. Malmö General Hospital S-214 01 Malmö, Sweden Author(s) Magnus Grabe	Document name DOCTORAL DISSERTATION	
	Date of issue 1984-01-12	
	CODEN: LUMEDW/(MEUS-1003)/1-66(1984)	
Sponsoring organization		
Title and subtitle Short antibiotic courses in transurethral prostatic resection		
Abstract Transurethral resection (TUR) has become the method of choice for treatment of obstructive prostatic enlargement. Infectious complications in terms of septicemia and upper urinary tract infections may jeopardize the postoperative period and bacteriuria is frequently recorded after TUR. To increase knowledge concerning the value of short antibiotic courses in the prevention of such complications, two randomized controlled clinical trials comprising 192 and 96 patients respectively were carried out, using a potent cephalosporin (cefotaxime). It was shown that a short perioperative antibiotic course significantly reduced the frequency of postoperative bacteriuria by protecting preoperatively non-bacteriuric patients from acquiring bacteriuria (prophylactic effect) and by eliminating bacteriuria in more than half of the preoperatively bacteriuric patients (therapeutic effect), compared to untreated control patients. The course also significantly protected against severe postoperative infectious complications. No such effects were registered for a short postoperatively scheduled course. The perioperative course did not influence long-term mortality but was associated with a lower frequency of late infectious events and postoperative urethral stricture formation and the prescription of supplementary antibiotics was lower. Gram-negative bacteria predominated (70-80%) and no noteworthy change of species distribution or sensitivity pattern was recorded during five years of use of cefotaxime. No significant influence on the Gram-negative faecal flora was observed and no emergence of resistant strains was recorded after the short antibiotic course. Recurrence or persistence of bacteriuria after TUR was explained by preoperative treatment with indwelling catheter, chronic prostatitis, chronic pyelonephritis or cancer of the prostate. Cefotaxime was found in therapeutically adequate concentration in serum, urine and prostatic gland after i.m. injection in urological patients.		
Key words Transurethral resection of prostate (TUR), antibiotic prophylaxis, septicemia, urinary tract infection, bacteriuria, cefotaxime, microbial resistance.		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language English
ISSN and key title		ISBN
Recipient's notes	Number of pages 66	Price
	Security classification	

DOKUMENTATABLAD enl SIS 61 41 21

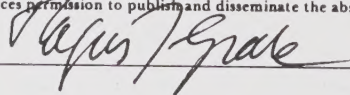
Distribution by (name and address)

Magnus Grabe, Department of Urology

Malmö General Hospital, s-214 01 Malmö, Sweden

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature



Date 84 01 12

From the Departments of Urology and Medical Microbiology
University of Lund, Malmö General Hospital, Malmö, Sweden

SHORT ANTIBIOTIC COURSES IN TRANSURETHRAL
PROSTATIC RESECTION

by

Magnus Grabe



Malmö 1984

Cover:

The Nāga, the seven headed serpent, god and guardian of water and treasure, forms his body in coils to make a seat for the *Buddha* in meditation position. *The Nāga* raises his great hood like an umbrella over his master's head to assure him protection.

In the *Khmer* art the *Nāga* symbolizes security and protection.

Statue from the 12th or 13th century (Museum of Phnom Penh, Kampuchea).

The present dissertation is based on the following publications:

- I. Grabe, M., Forsgren, A. & Hellsten, S. The effect of a short antibiotic course in transurethral prostatic resection.
Scan J Urol Nephrol. In press.
- II. Grabe, M., Forsgren, A. & Hellsten, S. Species distribution and antibiotic sensitivity of bacteria isolated pre- and postoperatively from patients undergoing transurethral prostatic resection.
Scan J Urol Nephrol. In press.
- III. Grabe, M., Forsgren, A. & Hellsten, S. A short antibiotic course given in conjunction with and after catheter removal consecutive to transurethral prostatic resection.
Scan J Urol Nephrol. In press.
- IV. Grabe, M. & Hellsten, S. Long-term follow-up after transurethral prostatic resection with or without a short perioperative antibiotic course.
In manuscript.
- V. Grabe, M., Andersson, K.-E., Forsgren, A. & Hellsten, S. Concentration of cefotaxime in serum, urine and tissues of urological patients.
Infection, 9, 154-158. 1981.

In the following presentation the publications will be referred to by Roman numerals I - V. The publications I, II, IV and V are based on a clinical trial referred to by *Study A* and the publication III on a trial denoted *Study B*. The results are summarized and discussed together with new and unpublished information.

CONTENTS

ABBREVIATIONS AND DEFINITIONS

INTRODUCTION

REVIEW OF EARLIER INVESTIGATIONS

Morbidity and mortality associated with TUR

Early postoperative complications

Late postoperative complications

Mortality

Comments

Factors reducing the rate of infectious complications after TUR

General methods

Antibiotics

AIMS OF THE INVESTIGATION

MATERIAL AND METHODS

Clinical trial

Patients and trial eligibility

Surgical procedure

Treatment schedule

Trial drug

Urine sampling

Susceptibility test

Bacteriological examination of the faecal flora

Determination of cefotaxime

Statistical methods

Comparability

RESULTS

Bacteriuria

Study A

Study B

Postoperative complications

Early postoperative complications up to one week

Complications observed between the second week and third month

Infectious events and complications observed after the third month

Mortality

Period of hospitalization

Study A

Study B

Microbial environment

Species distribution

Antimicrobial sensitivity

Bacteriological examination of the faecal flora

The trial drug

Cefotaxime concentration in serum

Cefotaxime concentration in urine

Cefotaxime concentration in prostate

Tolerance and adverse reaction

Comments

DISCUSSION

CONCLUSIONS

ACKNOWLEDGEMENTS

REFERENCES

PAPERS I - V

ABBREVIATIONS AND DEFINITIONS

The following abbreviations and definitions will be used in the text:

Abbreviations:

CFU/L: Colony Forming Units per Litre Urine.

MIC: Minimum Inhibitory Concentration.

TUR: Transurethral Resection of the Prostate.

UTI: Urinary Tract Infection.

Definitions:

Bacteremia: is defined as the transient appearance of bacteria in the blood stream (positive blood culture) without the establishment of a systemic infection.

Bacteriuria: is defined as the presence of $\geq 10^7$ CFU/L urine. Bacteriuria is divided in two subgroups according to the bacterial count:

- non-significant bacteriuria: 10^7 - 10^8 CFU/L.
- significant bacteriuria: $> 10^8$ CFU/L.

Furthermore the following terminology is used in relation to bacteriuria:

- *acquired bacteriuria*: is pre- and postoperatively acquired bacterial infection in urine in preoperatively non-bacteriuric patients.
- *persisting bacteriuria*: is the continuous presence of bacteriuria pre- and postoperatively in patients not receiving antibiotics in conjunction with TUR.
- *recurring bacteriuria*: is the reappearance postoperatively of the same bacterial strain as recorded preoperatively or of a new strain in patients receiving antibiotics in conjunction with TUR.

Epididymitis: is defined as a painful induration of the epididymis with or without fever and accompanied or not with bacteriuria.

Lower urinary tract infection: is bacteriuria associated with symptoms of cystitis.

Operative mortality: is defined as the mortality reported to occur within the first month after TUR, related or not to the operation.

Perioperative antibiotic course: is an antibiotic course initiated preoperatively and covering the operation and the postoperative period

according to a defined schedule.

Postoperative antibiotic course: is an antibiotic course started after the operation and according to a defined schedule.

Septicemia: denotes bacteremia accompanied by clinical systemic symptoms representing the establishment of a generalized infection.

Upper urinary tract infection: is defined as bacteriuria and fever (usually 38.5° for $\geq$ two days) associated with flank pain and/or systemic symptoms.

INTRODUCTION

In the late 1920's Stern (Stern, 1926) and McCarthy (McCarthy, 1931) introduced transurethral resection which has become the method of choice in most cases of obstruction due to hyperplasia and cancer of the prostate. Technical improvements in instruments, increased experience and skill among urologists, more accurate preoperative evaluation and preparation of the patients and progress in anaesthesia and postoperative care, have reduced the risks of surgery.

During the 20th century the change in population age structure has increased the number of elderly individuals in the community (Freedman & Berelson, 1974; Westoff, 1974). Consequently a greater number of men of 50 and above, susceptible to symptomatic prostatic enlargement will require TUR (Lytton, Emery & Harvard, 1968). The economic advantage of TUR over open prostatic surgery is also well established (Davis, 1931; Argyrou, Blandy, Gow, Singh, Tresidder & Vinnicombe, 1974). For the patients TUR has meant increased security and less discomfort compared to open surgery because of a lower frequency of postoperative complications, shorter hospital stay and earlier return to work and daily activities (Rutishauser, Schubarth, Graber, Baumann & Leibundgut, 1974; Lund & Dingsør, 1976; Chilton, Morgan, England, Paris & Blandy, 1978).

Severe infectious complications following urological instrumentations are well-known. One hundred years ago Sir Andrew Clark presented some 'remarks on catheter fever' and described his own and other people's experience of patients who most likely died from septicemia after catheterization (Clark, 1883). In 1909 Jacob drew attention to *E. coli* septicemia. He reviewed 39 patients out of which 18 died (Jacob, 1909). Felty reported a mortality rate of 32 per cent in 25 cases of coliform septicemia. The genito-urinary tract was the portal of entry in the majority of the cases (Felty & Keefer, 1924). Scott published a careful study of 82 urological patients with positive blood culture out of whom 15 died (18%). In 51 patients (62%) infection developed in the early postoperative period (<72 hours) and in 80 per cent of the cases operation on the urethra including the prostatic portion was the probable portal of entry (Scott, 1929). Waisbren studied 29 cases of bacteremia due to Gram-negative pathogens. Nineteen of these (66%) were due to catheterization or operations on the urinary tract. Fifteen patients showed a 'shock-like picture' and are apparently the first reported association of Gram-negative bacteremia and shock (Waisbren, 1951) (Table I). Considering 232 cases of septicemia originating from urinary tract surgery, Richaud reported that operations on the prostate and

proximal urethra represented 34 per cent of them (Richaud, 1976).

Also after TUR infectious complications are a matter of concern and have been extensively discussed in the urological literature. Numerous methods have been investigated to reduce their incidence. The present studies were undertaken to increase knowledge of the value of antimicrobial agents in TUR.

Table I: *Gram-negative septicemia*. Frequency of urogenital tract disease or instrumentation as source of septicemia and mortality rate.

Authors	No patients	Urogenital tract as source (%)	Overall mortality (%)
Felty & Keefer (1924)	25	84	32
Waisbren (1951)	29	77 a)	17
McCabe & Jackson (1962)	173	49	42
Altemeier et al. (1967)	337	57 b)	58
DuPont & Spink (1969)	655 c)	45	49
Quintiliani et al. (1978)	326	14 d)	no data
Svanbom (1979)	110 e)	27	26
Kreger et al. (1980)	612	34	25 f)

a) 19/29 (66%) after instrumentation

b) 91/337 (27%) associated with operation or instrumentation

c) only adult cases

d) 30/326 (9%) definitely associated with instrumentation. 1/30 (3%) died. 16/326 (5%) other sources possible besides urogenital tract manipulation. Mortality 75%.

e) only bacteriological documented cases

f) 15 % fatal outcome in urological patients.

Table II. Frequency of *acquired bacteriuria* after TUR in patients with or without antibiotics at time of surgery.
Clinical trials until 1979.

Author	Antimicrobial agent	With antimicrobial agent		Without antimicrobial agent		p value
		No patients investigated	Acquired bacteriuria (per cent)	No patients investigated	Acquired bacteriuria (per cent)	
Genster et al (1970)	urine disinfectants	50	56	43	70	N.S.
	antibiotics	87	40			p<0.02
Jackaman et al (1975)	-	-	-	34	18	-
Gonzales et al (1976)	cephalotin	41	0	49	41	p<0.01
Morris et al (1976)	kanamycin + co-trimazole	42	5	53	26	p<0.01
Colliste et al (1978)	-	-	-	76	32	-
Gibbons et al (1978)	kanamycin	50	14	50	20	N.S.
Matthew et al (1978)	nitrofurantoin	42	0	40	32	p<0.01

N.S. = Non-significant.

REVIEW OF EARLIER INVESTIGATIONS

Morbidity and mortality associated with TUR

Early postoperative complications:

Infectious complications following TUR are essentially the following:

1. Lower urinary tract infection and asymptomatic bacteriuria
2. Upper urinary tract infection
3. Bacteremia and septicemia
4. Epididymitis

1. Lower urinary tract infections and asymptomatic bacteriuria: Helmholtz demonstrated in man that the distal urethra up to a distance of 6 cm from the meatus is colonized with both Gram-negative and Gram-positive bacteria (Helmholz 1950). Bacteria may gain entry into the bladder through catheterization (Guze & Beeson, 1956), either by ascending within the catheter lumen (Kunin & McCormack, 1966; Garibaldi, Burke, Dickman & Smith, 1974) or outside the catheter along the mucosa (Brehmer & Madsen, 1972). The prostate is also shown to harbour pathogens (Kidd & Burnside, 1965; Morris, Golovsky, Guinness & Maher, 1976; Landes, Medenbach & Lee, 1976) and permanent drainage with an indwelling catheter to predispose the gland to inflammation and bacterial growth (Danielsson, 1978). Another major source for bacteriuria is chronic prostatitis (Meares & Stamey, 1972) which is known to prevail in some patients with prostatic enlargement and prostatic calculi (Stamey, 1981). Therefore, in a substantial number of patients, TUR is carried out in an infected operation field.

Almost all preoperatively bacteriuric patients remained bacteriuric after surgery without antibiotics (Plorde, Kennedy, Bourne, Ansell & Petersdorf, 1965; Genster & Madsen, 1970). According to investigations carried out prior to 1979, preoperatively non-bacteriuric patients acquire bacteriuria after TUR in frequencies between 18 and 70 per cent (Table II). Some investigations suggest that the frequency of bacteriuria decreases spontaneously during the month following TUR after normalization of voiding (Plorde et al; Genster et al). Nevertheless the results are difficult to interpret because of lack of information concerning the prescription of antibiotics during this postoperative period of time.

2. Upper urinary tract infection: In most reports a precise definition of upper urinary tract infection is lacking. Fever, usually about 38°C, is often

referred to as a sign of infectious complication. However ascending urinary tract infection including pyelonephritis is described as emerging after TUR in 0.1 to 6 per cent (Creevy & Feeney, 1954; Holtgrewe & Valk, 1962; Bandhauer & Madersbacher, 1969; Melchior, Valk, Foret & Mebust, 1974; Morris et al).

3. *Bacteremia and Septicemia*: *Bacteremia*, defined as a temporary appearance of bacteria in the blood stream without the establishment of a generalized infection (Svanbom, 1979), is well-known after instrumentation such as cystoscopy and dilatation of the urethra (Barrington & Wright, 1930; Mitchell, Slade & Linton, 1962; Quintiliani, Cunha, Klimek & Maderazo, 1978) as well as after catheter removal, especially in patients with infected urine (Slade, 1958).

Bacteremia following TUR is described in various proportions: 10 - 57 per cent (Table III). The frequency is higher in preoperatively bacteriuric compared to non-bacteriuric patients.

Table III: *Bacteremia* after TUR

Author	Year	No. patients	Per cent
Biorn et al	1950	106	12
Creevy et al	1954	102	11*
		256	57**
Kidd et al	1964	47	11
Sullivan et al	1973	77	10*
		77	21**
Hofstetter et al	1977	169	28*
Robinson et al	1980	56	27
Robinson et al	1982	100	36

*preoperative urine culture negative
**preoperative urine culture positive

Septicemia, defined as persistence of bacteria in the blood stream, accompanied by a general reaction and the establishment of a systemic infection (Svanbom, 1979), is recognized as the most serious hazard following manipulation of the urinary tract in man. Nevertheless septicemia is reported in much lower proportions than bacteremia after TUR (0.7-6.1%) as shown in Table IV.

Finally bacterial endocarditis is described as a complication to TUR (Merritt, 1951).

Table IV: *Septicemia* after TUR

Author	Year	No. patients	Septicemia (per cent)
Bandhauer et al	1969	1444	0.7
Richaud	1976	221	1.4
Morris et al	1976	101	4
Hofstetter et al	1977	169	4
Cafferkey et al	1982	179	6.1*
Murphy et al	1983	1604	1.1

*preoperative urine culture positive.

4. *Epididymitis*: Epididymitis is reported in frequencies from 0.2 to 6.5 per cent postoperatively without vasectomy (Creedy et al; Bandhauer et al; Singh et al). This complication usually appears a few weeks to months after TUR.

Late postoperative complications:

In addition to persisting bacteriuria with or without symptoms and epididymitis, a well recognized complication is *stricture* of the urethra or the bladder neck, which is observed in frequencies ranging from 1 to 15 per cent (Bandhauer et al; Lentz, Mebust, Foret & Melchior, 1977; Hart & Fowler, 1981). Many reasons for postoperative stricture formation have been discussed such as insufficient preoperative calibration of the urethra, too large instruments, lengthy resections and urinary tract infections (Holtgrewe & Valk, 1964; Madersbacher & Marberger, 1971; Lentz et al). Only in bladder neck stricture formation has a common feature been found in terms of low weight of the resected prostatic specimen (Robinson & Greene, 1962; Holtgrewe et al).

However no correlation has been observed between stricture formation and bacteriuria (Lentz et al; Hart et al) or the type of catheter used in the postoperative drainage (Hart et al).

Mortality:

Mortality following open prostatic surgery is reported in historical material

Table V. *Mortality* associated with TUR (operative mortality).

Author	Year	No of patients	Mortality (per cent)	Cause of death (number)
Davis	1931	200	0	-
Alcock a)	1932	400	6.5	-
Nesbit b)	1946	2425	1.8	-
Thompson	1951	23938	1.1	-
Creedy	1951	1000	0.6	-
Bergman et al	1955	1000	1.8	cardiovascular (9) renal failure (3) prostatic cancer (3) others (3)
Holtgrewe et al	1962	2015	2.5	cardiovascular (36) pulmonary (5) renal failure (3) sepsis (4) others (3)
O'Flynn	1967	1597	1.2	-
Bandhauer et al	1969	1444	3.3	cardiovascular and pulmonary (26) upper UTI (10) sepsis (1) renal failure (4) others (7)
Singh et al	1973	935	1.3	cardiovascular (5) pulmonary (4) haemorrhage (3)
Melchior et al	1974	2223	1.3	cardiovascular (16) pulmonary (2) renal failure (3) others (9)
Rutishauser et al	1974	519	0.8	cardiovascular and pulmonary
Obrant	1976	186	0	-
Lund et al	1976	532	0.4	cardiovascular and pulmonary
Bandhauer et al	1977	1014	0.7	cardiovascular (5) pulmonary (1) agranulocytosis (1)
Sach et al	1977	78	3.8	-
Blandy	1978	1939	1.1	-
Chilton et al	1978	1004	1.0	cardiovascular (5) pulmonary (4) unknown (1)
Grabe	1983	410	0.7	cardiovascular (1) septicemia (1) cancer (1)

a) quoted by Creedy (1954). b) quoted by Creedy (1951).

between 3.2 (Young & Davis, 1926) and 5.4 per cent (Hunt & Walters, 1938), and remained unchanged for years, i.e. around 5 per cent (Creedy, 1951). In a post mortem analysis of 229 deaths after prostatectomy from the era before antimicrobial agents, Tenney quoted by Creedy, found that 65 per cent of deaths were associated with severe infections (Creedy et al, 1954). *Transurethral resection of the prostate* is a safer method. Davis observed no fatality among 200 patients (Davis, 1931), Alcock had a mortality rate of 6.5 per cent but Nesbit only 1.8 per cent (quoted by Creedy,1951). Thompson reviewed 23,938 patients undergoing TUR during 25 years (1933 - 1957) and found a mortality rate of 1.14 per cent (Thompson, 1951). Following the introduction of isotone irrigation solution during TUR, a factor considered to improve safety in this operation and the more extensive use of antibiotics, different studies demonstrate a mortality rate ranging from 0.6 to 3.3 per cent with an average mortality rate of 2.0 (142 deaths in 7,056 patients). Mortality rate in material from the 1970's ranges from 0.4 to 2.3 per cent (Table V).

While in previous reports infectious complications are mentioned as the cause of death in a significant number of cases (Alcock, 1932; Creedy, 1951; Creedy et al; Bandhauer et al), later studies present convincingly comparable figures regarding the cause of death, mainly in terms of cardiovascular and respiratory complications. There are few reported fatal infectious events (Table V and VI).

Most deaths are related to advanced age, i.e. patients over 70 years. Concomitant cardiovascular, respiratory, renal or metabolic diseases increase operation risks (Singh et al; Sach & Marshall, 1977).

Table VI: *Death* from septicemia after TUR

Author	Year	No. patients	Death (per cent)
McLaughlin et al	1948	561	1.0
Thompson	1939	1200	0.5
Creedy et al	1954	888	0.9
Holtgrewe et al	1962	2015	0.2
Bandhauer et al	1969	1444	<0.1
Melchior et al	1974	2223	<0.1
Cafferkey et al	1982	179	0.6
Murphy et al	1982	1604	0.2

Comments:

Due to differences in study design, material, diagnostic criteria and definitions the interpretation of literature data is difficult and deserves a few comments.

Fever is often used as a sign of infection. However, elevation of the body temperature appears not to be a valuable criterion for infection, because a slight elevation to about 38°C can be observed after TUR in seemingly not infected patients. It has been suggested that tissue products entering the blood stream can cause transient temperature elevation (Creedy et al; Wear & Haly, 1973).

Bacteriuria is often asymptomatic postoperatively and its significance in the long term in prostatectomized patients is not sufficiently studied.

Bacteremia is frequently observed after TUR, principally in preoperatively bacteriuric patients although non-bacteriuric subjects cannot be disregarded (Table II). Bacteremia is usually transitory but may develop into an established systemic infection especially in elderly patients. Mortality due to *septicemia* increases substantially after 65 years of age (Br Med J. 1975, 1, p. 634).

Because of the potential preventing role of antibiotics against bacteremia, septicemia and ascending urinary tract infections following TUR, an appropriate policy regarding the use of antimicrobial agents in conjunction with this operation is essential.

Factors reducing the rate of infectious complications after TUR

General methods:

Preoperative skin cleaning, sterilized instruments and sterile peroperative irrigation solution are fundamental in the aseptic operative procedure. So is the aseptic handling of the postoperative catheter treatment period. Nevertheless postoperative bacteriuria and potential severe infectious complications may follow. Numerous methods have been assessed to reduce postoperative bacteriuria.

Advances were made by the introduction of a *sterile closed drainage system* with or without an antiseptic solution in the collecting bag (Kunin & McCormack, 1966; Webb & Blandy, 1968) in addition to careful continuous aseptic handling of the catheter (Desautels, 1960). However a *continuous irrigation* of the bladder was not proved to be better than drainage only (Bastable, Peel, Birch & Richards, 1977; Warren, Platt, Thomas, Rosner & Kass, 1978).

Lubrication of the urethra with an antibacterial agent (Kunin & Finkelberg, 1971), antibiotic-impregnated catheters (Butler & Kunin, 1968) and cleaning of the meatus with a disinfectant (Britt, Burk, Miller, Steinmuller & Garibaldi, 1976) have been tried in an attempt to prevent ascending infections from the distal urethra and meatus to reach the bladder through the instrumentation and the catheter but without noteworthy effect on the infection rate (Garibaldi, Burk, Britt, Miller & Smith, 1980).

Transurethral prostatectomy *without catheter* drainage has been assessed without the expected success. Intermittent catheterization and indwelling catheter postoperatively could not be avoided in a substantial number of patients. Therefore urinary tract infection and/or septicemia could not be avoided. Cass reported 24 cases of severe infections in 202 patients undergoing TUR without catheter drainage (Cass, 1969).

Forced diuresis was suggested as a reasonable method in the treatment control of the postoperative bleeding and clot formation as well as to reduce the frequency of bacteriuria (McKelvie, 1962; Essenhigh, Clayton & Taha, 1970). There is a direct correlation between the *time of catheterization* and the rate of infections (Kunin et al; Symes, Hardy, Sutherns & Blandy, 1972). It is clear that the shorter the postoperative period of catheterization, the lower the risk of bacteriuria. Short postoperative catheterization is nowadays routine in urological departments.

Finally *shaving of the patient* prior to transurethral surgery was found to be of no advantage (Frazer, MacPherson & Panagakis, 1978).

Antibiotics:

Antibiotics were introduced in transurethral surgery in 1938 by Gaudin (Gaudin, Zide & Thompson, 1938). Many studies have been performed since then to assess the efficacy of antibiotics in TUR. Most antimicrobial agents, i.e. sulfonamides, penicillins, aminoglycosides, cephalosporins, nitrofurantoin and urine-disinfectants such as methenaminhippurate have been used. The antibiotic schedules have usually been given to cover the operation and the postoperative period extending from one to several weeks. As pointed out in two review papers the inconsistency of the investigations is noteworthy (Berger & Nagar, 1978; Chodak & Plaut, 1979). The studies have differed in design (prospective or retrospective studies, allocation by randomization or not, controls or not, follow-up schedule), in material and operation procedures (both open and transurethral prostatectomy, often reviewed together) and in diagnostic criteria and definitions (i.e. bacterial counts). A few trials demonstrated the efficacy of antimicrobial agents in protecting patients undergoing TUR or open prostatectomy from acquiring bacteriuria, bacteremia, and severe postoperative infectious complications (Plorde et al; Gonzales et al; Hills, Bultitude & Eykyn, 1976; Morris et al). Other trials concluded that routine antibiotics in TUR were unnecessary and even undesirable (Genster et al; McGuire, 1974; Gibbons et al).

Thus at the time when the present study A was initiated the value of antimicrobial agents in transurethral surgery was controversial.

AIMS OF THE INVESTIGATION

The aims were:

1. To study whether a potent antimicrobial agent (cefotaxime) given parenterally in conjunction with TUR and timed either perioperatively (I) or postoperatively (III) reduces:
 - a) the frequency of postoperative bacteriuria
 - b) the incidence of postoperative severe infectious complications in terms of septicemia and upper urinary tract infections.
2. To investigate the long-term outcome of patients with or without a perioperative antibiotic course (IV).
3. To analyse the distribution of isolated bacterial species and their sensitivity to different antibiotics and to correlate bacteriological and clinical data (II) (III).
4. To subject five years of use of cefotaxime in prophylaxis and treatment of severely ill patients to a critical analysis regarding the development of resistance to the drug.
5. To determine the concentration of cefotaxime in serum, urine and prostate (V).

Clinical trial:

A balanced *randomization* was chosen for the present two clinical trials including treated test groups and untreated control groups. In a first *study A* (I) the patients were followed for 6 weeks postoperatively. In a second *study B* (III) the patients were observed for infectious complications subsequent to TUR and followed for four months regarding urine culture. Records were kept on designed protocols and information concerning the intergroup comparability, postoperative care, infectious complications, subsequent treatment, results of urine culture and required laboratory data were collected. Later a retrospective analysis of the long-term outcome of the patient in study A was made (IV). Details are discussed in *material and methods* in each paper (I, III, IV).

A third, currently, running clinical trial (study C) designed like study A, compares cefotaxime parenterally to the oral combination pivampicillin/pivmecillinam (Miraxid). Preliminary bacteriological data are presented and compared to earlier studies A and B.

Patients and trial eligibility :

All patients, regardless of age, admitted to the urological department for transurethral prostatic surgery due to hyperplasia or cancer of the prostate, entered the trials. Patients with or without indwelling catheter, bacteriuric or not were considered equally eligible. Patients with concomitant disease were qualified for TUR after approval by the department of anaesthesiology.

Excluded from the trials were only patients with hypersensitivity to penicillin or cephalosporins, patients who had received antibiotics during the week before TUR and patients with serum creatinine $> 115 \mu\text{mol/l}$.

One hundred and ninety-two patients were included in study A (I). Ninety-eight were randomly allocated to the test group (cefotaxime group) and 94 to the control group. In study B (III), comprising 96 patients, the distribution was 47 to the cefotaxime group and 49 to the control group.

Surgical procedure:

TUR was performed in one operation centre using a standardized technique by urologists, members of the staff. Spinal anaesthesia was given according to our hospital's routine. After initiation of anaesthesia intravenous Dextran 70 infusion was started. Peroperatively the urinary bladder was irrigated with sterile glycine (2.2%). Forced diuresis was induced during the operation by intravenous injection of 40 mg of furosemide. High diuresis was maintained during the following 24 hours by intravenous infusion of usually 3 - 6 litres of crystalloid solution (Ringer-glucose 2.2%; fructose 15%-glucose 5.5%) to which was added 20 mg of furosemide per litre. The total of furosemide intravenously administered was generally 80 - 120 mg. Closed sterile bladder drainage was maintained postoperatively. No external irrigation was given unless required, because of heavy postoperative bleeding. The indwelling catheter was removed on the first or second postoperative day except for a few patients requiring a longer period of catheterization. The patients were discharged one or a few days after catheter removal.

Treatment schedule:

Study A: In the first 71 patients of the cefotaxime group the drug was administered in a dosage of 0.75 gram twice a day by intramuscular injection and the following 27 patients received one gram once a day. The first dose of cefotaxime was given on the evening before TUR, the second at the time of the preoperative medication and the final dose on the day when the indwelling catheter was removed. If catheterization was prolonged the treatment with cefotaxime was consecutively prolonged to cover the period of catheterization, but not for longer than one week. The patients in the control group received no antibiotics unless clinical infectious complications arose.

Study B: One gram of cefotaxime was given intramuscularly every 12 hours to a total of 3 grams with the first dose given on the day of and just prior to the removal of the indwelling catheter. As in study A the patients in the control group received no antibiotics unless infectious complications arose.

In both studies whenever the patients showed bacteriuria, symptomatic or not after the 6-week control, they were usually given an antibiotic according to the sensitivity pattern.

Trial drug:

Cefotaxime was chosen because of remarkable high activity against urinary tract pathogens including *Klebsiella*, *Serratia marcescens* and to some extent *Pseudomonas aeruginosa* (Hamilton-Miller, Brumfitt & Reynolds, 1978). The initial assessment indicated a low toxicity of the drug.

Urine sampling:

Samples for urine cultures were taken 1-3 days before the operation and on the day of postoperative catheter removal (study A) or on the day of discharge from hospital (study B). Further cultures were taken at 10 days and 6 weeks postoperatively in both studies and an additional fourth month culture sample was analysed in study B.

Cultures were made from clean, voided mid-stream urine with an incubation time of 4 hours when possible. Urine samples obtained from indwelling catheters were collected by aspiration from the tube after cleaning with a wet swab and after clamping of the tube for approximately 30 minutes. The samples were immediately refrigerated and bacteriological processing usually initiated within 1-2 hours. Cultures were performed by a routine quantitative assay on blood agar plates and a variant of LSU-agar (medium 32)(Juhlin & Ericsson, 1961). Isolated bacteria were identified with conventional biochemical tests (Cowan & Steele, 1970) and stored as nutrient agar stab cultures.

The number of patients in whom urine cultures were assessed pre- and postoperatively during the follow-up are described comprehensively in each trial respectively (I) (III).

Susceptibility test:

The sensitivity of isolated bacteria to antibiotics was assessed immediately after isolation using a disc diffusion method (Ericsson & Sherris, 1971) on PDM-agar (AB Biodisk, Stockholm). After the clinical study was completed the minimum inhibitory concentration (MIC-value) for the isolated bacteria was determined with an agar dilution method (Forsgren, 1981). The medium used was PDM-agar and the inoculum consisted of a 4-hour-culture diluted in saline to a concentration of 10^7 bacteria per litre and applied to the surface of the agar in 1-2 μ l quantities with the aid of a multipoint inoculator. Ampicillin (AS-360 Leo, Denmark), mecillinam (81 12 10 Leo, Denmark), cephalexin (81A 729, Eli

Lilly), cefotaxime (Hoechst 65), gentamicin (81 B 2602, Schering Corp.), nalidixic acid (214/554 Sterling Wintrops), nitrofurantoin (87 367 Pharmacia, Sweden) trimethoprim (27 657-52, Kabi, Sweden), co-trimazin (trimethoprim/sulfadiazin:18%/82%) (82 01 11, Astra, Sweden) were tested. The evaluation of resistance and sensitivity respectively was based on the SIR-system (The Swedish Reference Group for Antibiotics, 1981). For co-trimazin a break-point of 8 μ l per ml was used.

Bacteriological examination of the faecal flora:

Examination of faecal flora was performed during 1983 according to the method described by Alestig & Lidin-Janson (1975). Rectal swabs were taken with the stick inserted about 4 cm from the anal skin surface. Each swab was put into a tube with a modified Stuart medium and placed in a refrigerator until the plating out was done, always within 4 hours.

The swab was first used for heavy inoculation on a 9 cm PDM agar plate (Antibiotic Sensitivity Medium, AB Biodisk, Stockholm, Sweden). The following antibiotic discs were placed on the agar surface: cefotaxime (15 μ g), ampicillin (10 μ g), mecillinam (10 μ g), miraxide (ampicillin 10 μ g + mecillinam 10 μ g). The swabs were also cultured on three separate peripheral areas on a 32-agar-plate (a variant of LSU agar; Juhlin & Ericsson, 1961) for the examination of colony forming Enterobacteriaceae and Pseudomonas. The three inoculates on the 32-agar-plate were thinned out by successive streaks with a platinum loop. The plates were incubated overnight at 37°C. From each of the three cultures on 32-agar the last colony growing from the successive streaks was selected for subculture as were colonies with the morphology of Gram-negative bacilli or yeast appearing within the zone of inhibition of sensitive *E. coli*. Bacteriological isolates were identified by using standard methods (Cowan & Steel, 1970). Antibiotic sensitivity was tested by the disc-diffusion method of Ericsson & Sherris (1971).

A rating system modified from Lidin-Janson (1977) was used for grading resistance to cefotaxime in the microbial flora of the rectum:

0: No cefotaxime-resistant Enterobacteriaceae or Pseudomonas were found. This usually corresponds to less than 1/1.000 colonies resistant to cefotaxime.

1: Cefotaxime-resistant Enterobacteriaceae or Pseudomonas appeared in the inhibition zone around the cefotaxime disc. However, all colonies from the 32-agar-plate were sensitive and as the dominating strain will be represented in 98 per cent of such samples (Lidin-Janson et al., 1977) a rating of one of them

will indicate that the dominant strain was probably sensitive to cefotaxime.

2: One or two of three randomly selected colonies were resistant. Thus the dominant strain was either sensitive or resistant.

3: All three randomly selected colonies were resistant to cefotaxime, as was probably the dominant strain.

Determination of cefotaxime:

Bioassay: Cefotaxime concentrations were determined by an agar well diffusion method using PDM-ASM agar, pH 7.2. The tests were made in plastic bioassay dishes, 24 cm x 24 cm (Nunc, Denmark), with an agar layer of approximately 4 mm. The test strain *Escherichia coli* ATCC 25992 was suspended in saline to 10^5 bacteria/ml and distributed over the plates. Excess suspension was sucked off immediately and the plates were dried for 60 min at 37°C. Wells 4 mm in diameter were punched out in the agar and filled to the brim with the specimens to be tested. The zone of inhibition was measured after 18 h at 37°C. Serum was tested undiluted or diluted 1:1 in normal pooled human serum. Urine was diluted in saline until the concentration was within the range of the assay. Tissue samples (approximately 200 mg) were thawed, weighed, minced with scissors and homogenized in an Ultra-Turrax homogenizer with 400 µl of phosphate buffered saline (PBS; 0.02 M phosphate buffer, pH 7.2 with 0.15 M NaCl) per sample. Fresh standard solutions of cefotaxime (range 0.3 to 40 µg/ml) were prepared for each test by diluting a fresh stock solution (1000 µg/ml of active substance) in saline, serum, urine, prostatic and renal tissue homogenate. All samples were assayed in duplicate. The tissue was investigated for blood contamination (Dr. A. Grubb, Dept. of Clinical Chemistry, Malmö General Hospital) using a spectrophotometric method. It was found that blood contamination did not exceed 5 % of the tissue weight.

Chemical assay: Cefotaxime concentrations in serum were determined using a high pressure liquid chromatographic (HPLC) method. 200 µl of internal standard (0.1 µg/ml cefuroxime) and 3 ml of methanol were added to 1 ml of patient serum. After mixing, the sample was kept at room temperature for 15 min and then centrifuged for 10 min at 3,700 rpm. The supernatant was decanted and filtered through a Millipore filter. Twenty µl of the filtrate were injected into a chromatograph (Waters Assoc.) equipped with a solvent delivery system model 6000 and an absorbance detector. Separation was performed on a Boadapak C₁₈ column, and a mixture of acetic acid, water and methanol (1:72:27) was used as a mobile phase. Absorbance was measured at 254 nm. The intra- and interassay variation

of the method was tested on plasma samples containing 5 and 15 $\mu\text{g/ml}$ of cefotaxime. Variation was found to be about 2 %. All patient samples were analysed in duplicate.

Statistical methods:

Standard descriptive statistical methods were used. Testing for significance was performed by the 2x2 Chi-square test and the Fisher's exact test. Means were compared according to normal and t-distribution as required (Colton, 1974). The McNemar test for significance of change was used to compare changes in the frequency of bacteriuria in urine culture before and after operation in the treated and untreated group respectively. Comparing means in the biological assays were performed with the Wilcoxon matched pairs signed ranks test (Siegel, 1956). Two-sided test was chosen. Calculations were performed using a Texas Instrument Ti 58 C including a solid state software TM 'applied statistics' module or with a Hewlett-Packard HP 9845 with a NHSP statistical package.

Comparability:

In both studies A and B, the cefotaxime and the control groups were comparable in terms of concomitant disease, operation procedure and postoperative care including postoperative catheter treatment period, frequency of malignancy and weight of the resected prostate and total and postoperative period of hospitalization (Table VII and XIII). In study A the age of the patients was evenly distributed, but in study B a statistically significant difference was observed ($p=0.03$)(Table VII).

Table VII. *Clinical data** on 192 (study A) and 96 (study B) patients undergoing TUR.

Clinical data	Study A		Study B	
	cefotaxime group (n=98)	control group (n=94)	cefotaxime group (n=47)	control group (n=49)
Age, years (mean & range)	71.7 (56-86)	70.9 (39-88)	70.7 (53-84)	73.8 (60-88)
No (%) with prostatic cancer	20 (20)	26 (28)	6 (13)	11 (22)
No (%) with indwelling catheter before operation	41 (42)	29 (31)	23 (49)	29 (59)
Weight of the resected prostate g (mean & range)	16.1 (2-70)	15.6 (2-113)	24.1 (2-116)	22.9 (3-65)
No of days with postoperative indwelling catheter (mean)	1.8	2.0	1.9	1.8

* Period of hospitalization presented in Table XIII.

RESULTS

The effects of a short perioperative antibiotic course were investigated in a first clinical trial started in 1978 and referred to by *study A*. The clinical and bacteriological results are presented in the papers (I), (IV) and (II) respectively. In 1981 a second clinical trial referred to by *study B* was carried out to investigate the effects of a short postoperative antibiotic course (III). A third, currently running trial, started in 1982, is referred to by *study C*. No results from this trial have yet been published but preliminary bacteriological findings are presented together with corresponding data from study A and B.

An antibiotic with high *in vitro* activity against most pathogens encountered in the urinary tract in patients undergoing TUR was chosen (cefotaxime). During the trials pharmacokinetic and toxicity studies were carried out (V).

Bacteriuria (I) (III)

Seventy out of 192 (36%) patients in study A and 52 out of 96 (54%) in study B required catheter treatment prior to TUR. Ninety-two per cent (89% in study A and 96% in study B) of the patients with an indwelling catheter before TUR and 15 per cent of preoperatively non-catheterized patients had bacteriuria. Postoperative bacteriuria in all patients can be divided in *acquired bacteriuria* in preoperatively non-bacteriuric patients and *persisting or recurring bacteriuria* in preoperatively bacteriuric patients.

Table VIII presents the frequency of bacteriuria in *all patients* before operation and postoperatively at catheter removal (study A) or hospital discharge (study B), at 10 days and six weeks respectively.

Study A:

In the cefotaxime group, the frequency of bacteriuria in *all patients* was reduced from 43 per cent preoperatively to 16 and 18 per cent respectively at 10 days and 6 weeks postoperatively. The corresponding figures for the control group were 40 per cent preoperatively and 54 and 42 per cent respectively during the follow-up.

In the cefotaxime group five out of 44 (11%) patients *without bacteriuria before operation* developed bacteriuria (all non-significant) at any time postoperative and none required treatment. In the control group 22/38 patients

Table VIII. Frequency of *bacteriuria* pre- and postoperatively (percent) in study A and B in the cefotaxime and control groups respectively.

Period	Study A		Study B		p value
	cefotaxime group (n=92) a)	control group (n=87)	cefotaxime group (n=44)	control group (n=46)	
Preoperative	43	40	48	63	
Postoperative					
1-4 days b)	1	60	0	52	p<0.001
10 days	16	54	38	60	p<0.001
6 weeks	18	42	33	50	p<0.01
4 months	-	-	31	38	p>0.1

a) Number of patients with initial urine culture available

b) At catheter removal (study A) and discharge (study B).

Table IX. Number of patients (per cent) *non-bacteriuric* pre- and postoperatively throughout the observation period and distribution of *acquired bacteriuria* according to the bacterial count.

	Study A		Study B	
	cefotaxime group (n=44) ^{a)}	control group (n=38)	cefotaxime group (n=20)	control group (n=17)
No (%) patients non-bacteriuric throughout follow-up	39 (89)	16 (42)	17 (85)	11 (65)
Acquired bacteriuria ^{b)}				
- non-significant	5 } (11)	7 } (58)	3 } (15)	2 } (35)
- significant	-	15	-	4

a) No patients non-bacteriuric preoperatively

b) Postoperatively at any time.

(58%) acquired bacteriuria at any time postoperatively (15 significant and 7 non-significant) and treatment with antibiotics was prescribed in 8 patients during the early follow-up (Table IX).

Bacteriuria was eliminated in 65 per cent at 10 days and 67 per cent at 6 weeks in 26 patients in the cefotaxime group with *preoperative significant bacteriuria*. In the control group (23) bacteriuria was eliminated in only 14 per cent at 10 days and 30 per cent at 6 weeks. Spontaneous cure without antibiotics was only recorded in 4 of these 23 patients (17%).

Study B:

On admission 48 per cent of the patients in the cefotaxime group and 63 per cent in the control group had bacteriuria. At 10 days and 6 weeks after TUR, the frequency of bacteriuria was 38 and 33 per cent respectively in the cefotaxime group, and 60 and 50 per cent respectively in the control group. Four months after TUR, bacteriuria was still present in 31 per cent in the cefotaxime group and 38 per cent in the control group (Table VIII).

In the cefotaxime group 17 out of 20 patients (85%) *without bacteriuria* preoperatively remained non-bacteriuric throughout the observation period. Three patients acquired a non-significant bacterial count requiring no treatment. In the control group 11 out of 17 (65%) preoperatively non-infected patients remained non-bacteriuric. Four patients acquired significant and two non-significant bacteriuria (Table IX) and 2 of them were treated with antibiotics.

Out of 21 *preoperatively bacteriuric* patients in the cefotaxime group bacteriuria recurred in 15 patients. In the control group postoperative bacteriuria persisted in 26 patients out of 29. In two patients bacteriuria was eliminated through antibiotic treatment and in one (5%) spontaneously.

Postoperative complications

Early postoperative complications up to one week (I) (III):

Table X demonstrates the early postoperative complications in both study A and B for the cefotaxime and the control groups respectively. In *study A*, septicemia and upper urinary tract infection were observed in 1 and 7 patients respectively, all in the control group. No severe infectious complication was seen in the cefotaxime group. The intergroup difference was statistically significant ($p < 0.01$). There were two patients with lower

Table X. *Early postoperative infectious complications* following TUR in 192 patients (study A) and 96 patients (study B)

Diagnosis	Study A		Study B	
	cefotaxime group (n=98)	control group (n=94)	cefotaxime group (n=47)	control group (n=49)
Septicemia	0	1	2	2
Upper UTI	0	7	1	5
Lower UTI	2	2	0	1
Total	2	10 ^{a)}	3	8 ^{b)}

a) $p < 0.02$. For septicemia and upper UTI the intergroup difference is $p < 0.01$.

b) $p > 0.1$.

Table XI. *Infectious complications* following TUR in 192 patients (study A) as recorded between 1 - 6 weeks and 6 weeks to 3 months.

Diagnosis	1 week - 6 weeks		6 weeks - 3 months	
	cefotaxime group (n=98)	control group (n=94)	cefotaxime group	control group
Septicemia	-	-	-	-
Upper UTI	-	-	-	-
Lower UTI	2	7	6	13
Epididymitis	1	1	1	-

	No patients	
Day	cefotaxime	control

-1	10	15
0	21	19
1	22	20
2	22	21
3	17	19
4	8	7
5	2	4

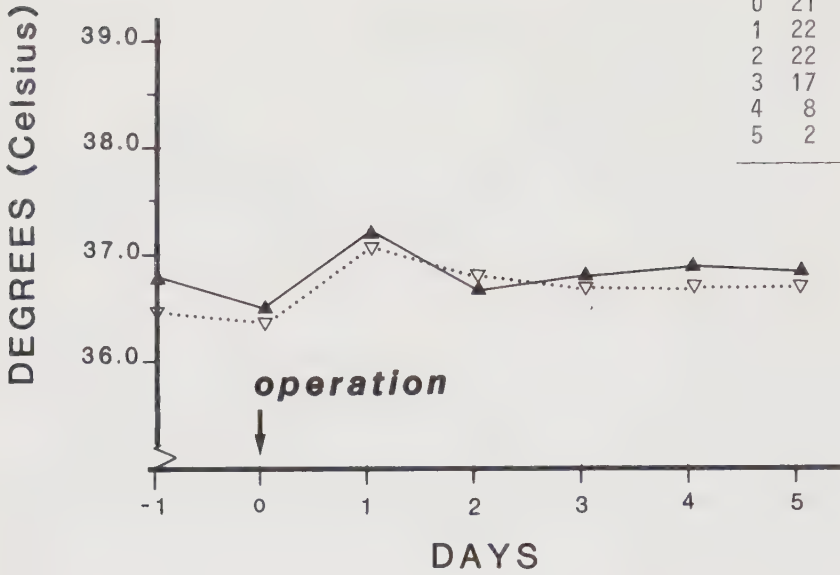


Fig 1 a. Morning body temperature in the cefotaxime group (▲—▲) and the control group (▽.....▽) respectively. The numbers in the table indicate the number of patients investigated.

	No patients	
Day	cefotaxime	control

-1	15	13
0	7	5
1	23	20
2	20	19
3	8	9
4	2	5
5	2	3

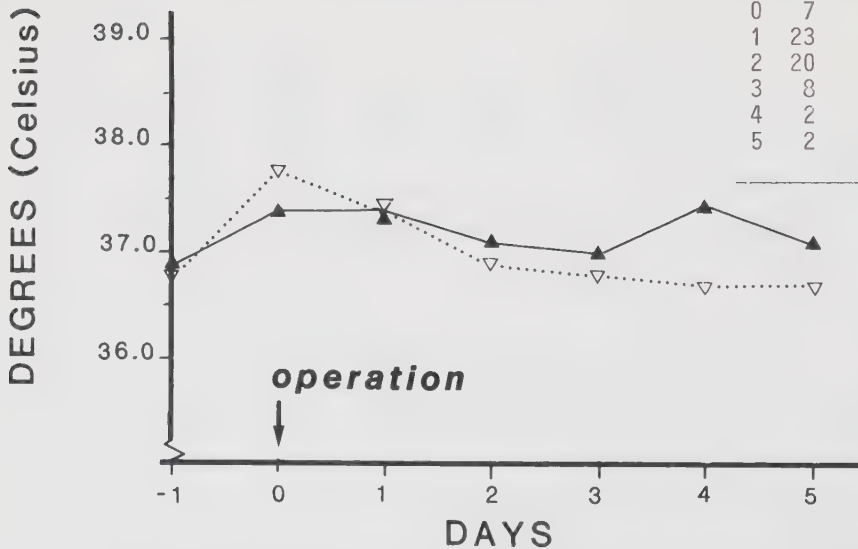


Fig 1 b. Evening body temperature in the cefotaxime and the control groups respectively. Symbols as in Fig 1 a. The number in the table indicate the number of patients investigated.

urinary tract infection in each group.

In *study B*, 4 cases of septicemia were observed, two in each group. Five out of 6 upper urinary tract infections appeared among the controls who received no antibiotics postoperatively (Table X).

Comments on body temperature (I): The morning- and evening temperatures were recorded in a limited sequential number of 22 patients in the cefotaxime group and 20 in the control group in study A. A slight elevation was noticed on the evening of the operation day which gradually returned to normal. No intergroup difference was seen between the groups neither for the morning- (Fig. 1a) nor for the evening temperature (Fig. 1b).

Complications observed between the second week and third month(I):

In study A no septicemia or upper urinary tract infection occurred during this period in any of the groups. Lower urinary tract infection appeared more frequently in the control group than in the cefotaxime group, and epididymitis was seen, one in the former and two in the latter group (Table XI).

Antibiotics were prescribed for a larger number of patients in the control group (32) than in the cefotaxime group (24) during the first three months.

Infectious events and complications observed after the third month (IV):

Late infectious events observed in the patients from study A are presented in Table XII. A larger number of infectious episodes were recorded in the control group compared to the cefotaxime group and more antibiotics were prescribed to the patients in the former (22) compared to the latter group (13). One case of septicemia and one severe upper urinary tract infection followed further endoscopy.

Chronic bacteriuria recurring in spite of repeated antibiotic courses was displayed in 11 patients (4 in the cefotaxime group and 7 in the control group). In a late follow-up (mean 3.5 years after TUR) bacteriuria was found in 24 per cent of the patients, evenly distributed between the two groups.

Stricture of the urethra or bladder neck was observed in only two cases in the cefotaxime group compared to 10 in the control group ($p = 0.03$).

Table XII. *Infectious events and stricture of the urethra or bladder neck observed after 3 months after TUR in 192 patients (98 in the cefotaxime group and 94 in the control group).*

Diagnosis	> 3 months after TUR	
	cefotaxime group	control group
Infections		
Septicemia	1	1
Upper UTI	1	3
Lower UTI	7	12
Epididymitis	-	1
Chronic bacteriuria	4	7
Stricture		
Meatus	1	3
Urethra (other parts)	-	4
Bladder neck	1	3

Mortality

Three fatal cases were observed, all in study A. The first patient (72 years) died of septicemia (*E. coli*), acute heart failure and postoperative bleeding. The second (55 years) died during operation probably of acute cardiac arrest. The third patient (76 years) died three weeks after the operation from metastasizing cancer of the rectum. All three patients belonged to the controls.

Period of hospitalization (I) (III)

Study A:

The total period of hospitalization was shorter for the patients in the cefotaxime group (mean 7.1 days) compared to those in the control group (7.95 days). The same observation was true for the postoperative period of hospitalization, i.e. 4.45 and 5.1 days, respectively. The intergroup difference was not statistically significant (Table XIII). The total period of hospitalization for the patients under 70 years (mean 6.5 days) was significantly lower compared to the patients 70 and over (mean 8.3 days; $p < 0.01$).

Cancer of the prostate did not influence the length of hospitalization.

Table XIII. Total- and postoperative period of hospitalization and period of hospitalization in relation to diagnosis (benign hyperplasia or cancer of the prostate) and preoperative treatment with indwelling catheter or not in 192 patients (study A) and 96 patients (study B) undergoing TUR. Number of days given in mean $\pm$ S.D.

	Study A		Study B	
	cefotaxime group (n=98)	control group (n=93) ^{a)}	cefotaxime group (n=47)	control group (n=49)
No of days of hospitalization (mean $\pm$ S.D.)	7.1 ($\pm$ 3.1)	7.9 ($\pm$ 4.6)	6.9 ($\pm$ 3.5)	8.5 ($\pm$ 5.7)
No of days of postoperative hospitalization (mean $\pm$ S.D.)	4.4 ($\pm$ 2.5)	5.1 ($\pm$ 4.0)	4.4 ($\pm$ 2.5)	5.9 ($\pm$ 4.8)
No days of hospitalization (mean $\pm$ S.D.)				
- benign hyperplasia	7.1 ($\pm$ 3.3)	8.1 ($\pm$ 4.8)	6.8 ($\pm$ 3.6)	8.2 ($\pm$ 5.6)
- cancer of prostate	7.4 ($\pm$ 2.6)	7.6 ($\pm$ 3.9)	7.5 ($\pm$ 3.1)	9.4 ($\pm$ 6.2)
No days of hospitalization (mean $\pm$ S.D.)				
- preoperative catheter	7.3 ($\pm$ 3.2)	8.6 ($\pm$ 5.4)	7.5 ($\pm$ 4.3)	9.9 ($\pm$ 6.6)
- no preoperative catheter	7.0 ($\pm$ 3.1)	7.6 ($\pm$ 4.1)	6.3 ($\pm$ 2.4)	6.5 ($\pm$ 3.2)
No days of hospitalization, patients with infectious complications (mean $\pm$ S.D.)	-	10.6 ($\pm$ 4.8)	8.7 ($\pm$ 1.2)	11.3 ($\pm$ 5.1)

a) one patient who died during the operation not included.

The period of hospitalization was slightly but not significantly prolonged in patients treated preoperatively with indwelling catheter. Nevertheless, patients with severe infectious complications spent a longer time hospitalized (mean 10.6 days) compared to all patients (mean 7.5 days).

Study B:

The total period of hospitalization was shorter for the patients belonging to the cefotaxime group (mean 6.9 days) compared to those in the control group (8.5 days) but without statistical significance ($p = 0.1$). The postoperative period of hospitalization was also shorter in the former group (4.4 days) compared to the latter (5.9 days; $p = 0.06$). Cancer of the prostate did not influence the hospitalization period in this study (Table XIII).

On the other hand the patients with preoperative catheter treatment were hospitalized longer (8.8 days) compared to the non-catheterized individuals (6.4 days; $p = 0.01$). The same was true for the postoperative period (6.0 and 4.2 days respectively; $p = 0.03$).

Also in this study, the patients with severe infectious complications were hospitalized for a longer period (10.5 days compared to 7.7 in all patients).

Microbial environment

The pathogens isolated preoperatively from the urinary tract of patients undergoing TUR during 1978 - 1979 (study A)(II), 1981 (study B)(III) and 1982/1983 (study C) have been reviewed. Focus is on species distribution and antimicrobial sensitivity pattern, emergence of resistant strains and analysis of the influence of cefotaxime on the faecal flora.

Species distribution:

In all three studies, the preoperative species distribution of isolated bacteria was similar (Table XIV). Gram-negative species predominated (67-80% of the isolated strains). *E. coli* was the most frequently isolated species followed by *Klebsiella*, *Enterobacter* and *Proteus* species. Among the Gram-positive (20-33%) enterococci and *Staphylococcus epidermidis* were the most frequently encountered species.

The pattern of the postoperatively acquired bacterial isolates was very similar to the preoperatively recorded species except for a slight increased rate of *Staphylococcus epidermidis* and enterococci (II) (III).

Table XIV. *Preoperatively isolated bacteria in study A, B and C respectively (number, per cent and median of MIC-values)*

Isolates	Study A			Study B			Study C		
	Number	Per cent	MIC(median)	Number	Per cent	MIC	Number	Per cent	MIC
<i>E. Coli</i>	15	18.5	0.06	14	24.6	0.125	35	26.7	0.125
<i>Proteus mirabilis</i>	11	13.6	0.06	4	7.0	0.03	12	9.2	0.03
<i>Klebsiella</i>	13	16.0	0.125	3	5.3	0.06	30	22.9	0.06
<i>Enterobacter</i>	9	11.1	1	8	14.0	0.5	18	13.7	0.25
<i>Other Proteus</i>	3	3.7	0.06	4	7.0	0.06	1	0.8	0.03
<i>Citrobacter</i>	1	1.2	n.d.	1	1.8	0.125	1	0.8	64
<i>Acinetobacter</i>	1	1.2	0.5	3	5.3	16.0	3	2.3	16
<i>Serratia</i>	-	-	-	1	1.8	0.06	-	-	-
<i>Pseudomonas</i>	4	4.9	32	-	-	-	5	3.8	16
Subtotal	57	70	-	38	67	-	105	80	-
<i>Enterococci</i>	11	13.6	8.0	7	12.3	128	10	7.6	2
<i>Staph. epidermidis</i>	8	9.9	1.0	9	15.8	0.5	10	7.6	1.0
<i>Staph. aureus</i>	5	6.2	4.0	3	5.3	4.0	4	3.0	2
<i>Staph. saprophyticus</i>	-	-	-	-	-	-	2	1.5	2
Subtotal	24	30	-	19	33	-	26	20	-
Total	81	100	-	57	100	-	131	100	-
Geometric mean*			0.28			0.26			0.20

n.d. = no data available

* enterococci not included.



Fig 2 a. Study A. Preoperative bacterial isolates in the cefotaxime and the control groups. Sensitivity testing is carried out for cefotaxime and ampicillin. Symbols above the dotted line indicate resistance to the drug according to the SIR system (The Swedish reference group for antibiotics). Symbols: E. Coli (◇); Klebsiella (□); Enterobacter (▽) Proteus mirabilis (○); other Proteus (△); Citrobacter (★); Acinetobacter (■); Serratia (*); Pseudomonas aeruginosa (▼); Enterococci (●); Staphylococcus epidermidis (◆); Staphylococcus aureus (▲).

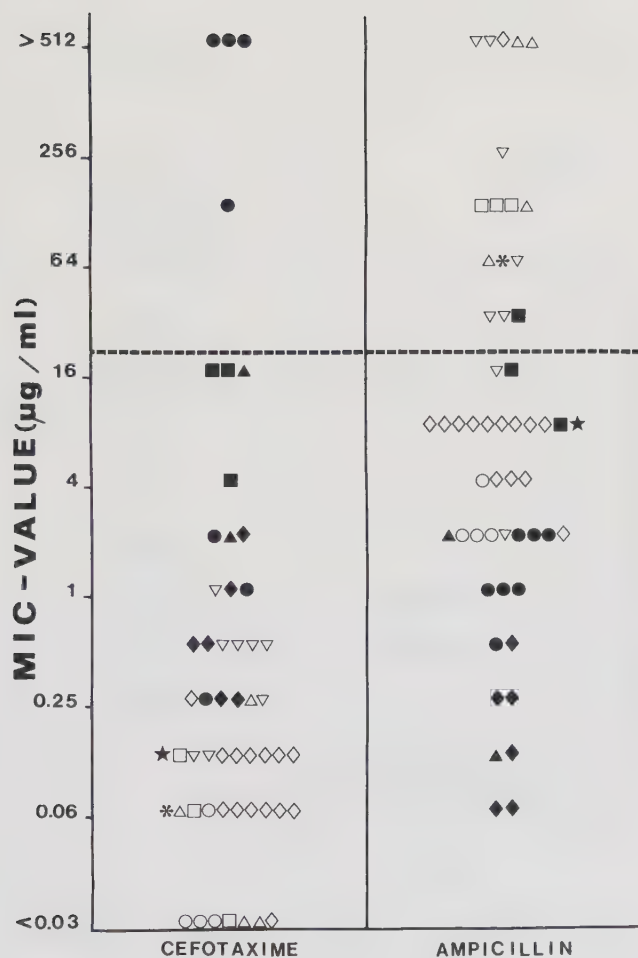


Fig 2 b. *Study B*. Preoperative bacterial isolates in the cefotaxime and the control groups. Sensitivity testing is carried out for cefotaxime and ampicillin. Symbols above the dotted line indicate resistance to the drug according to the SIR system. Symbols as in Fig 2 a.

Table XV a. Study A. *Size of the inhibition zones (mm) for cefotaxime before and after TUR for recurring and persisting bacteria in the cefotaxime group (10 strains) and the control group (21 strains).*

Group	Size of inhibition zones for cefotaxime (mm)		p value
	1 - 3 days before TUR	10 days/6 weeks after TUR	
Cefotaxime group			
mean($\pm$ S.D.)	34.8 ($\pm$ 1.6)	35.8 ($\pm$ 1.5)	N.S. ^{a)}
range	28 - 45	28 - 44	
Control group			
mean($\pm$ S.D.)	37.0 ($\pm$ 1.4)	36.6 ($\pm$ 1.5)	N.S.
range	21 - 48	19 - 47	

a) calculated by the Wilcoxon matched pairs signed ranks test.
N.S. = non-significant.

Table XV b. Study B. *Size of the inhibition zones (mm) for cefotaxime before and after TUR for recurring and persisting bacteria in the the cefotaxime group (13 strains) and the control group (14 strains)*

Group	Size of inhibition zones for cefotaxime (mm)		p value
	1 - 3 days before TUR	10 days/6 weeks after TUR	
Cefotaxime group			
mean($\pm$ S.D.)	40.6 ($\pm$ 1.2)	40.0 ($\pm$ 1.3)	N.S. ^{a)}
range	33 - 48	31 - 48	
Control group			
mean($\pm$ S.D.)	41.4 ($\pm$ 1.9)	41.1 ($\pm$ 1.8)	N.S.
range	29 - 55	29 - 53	

a) calculated by the Wilcoxon matched pairs signed ranks test.
N.S. = non-significant.

Antimicrobial sensitivity:

The sensitivity pattern of antibiotics commonly used for treatment of urinary tract infections, was tested on isolates from study A (II). A high degree of sensitivity was found for cefotaxime, gentamicin, trimethoprim, co-trimazine and the combination of pivampicillin and pivmecillinam.

In study B and C, the sensitivity testing was restrained to cefotaxime, the trial drug, and to ampicillin, a drug commonly prescribed in our department and here used as reference.

The sensitivity pattern and the MIC-values for the individual bacterial isolates collected from men undergoing TUR remained unchanged during 5 years of utilization of cefotaxime, as expressed through the MIC-values (median) and the geometric mean (Fig. 2a-c and Table XIV).

Many strains of enterococci and *Pseudomonas aeruginosa* were primarily resistant to cefotaxime. No emergence of new resistant strains were observed.

The inhibition zones for cefotaxime of the bacterial strains isolated both pre- and postoperatively from the patients in the cefotaxime group (recurring bacteria) were 34.8 and 35.8 mm respectively in study A (Table XVa) and 40.6 and 40.0 mm respectively in study B (Table XVb). All strains were sensitive before and after treatment. The size of the inhibition zone of individual strain was not markedly influenced by the antibiotic course and there was no statistically significant change before and after the course in all investigated bacteria.

In the control groups (persisting bacteria) the diameter of the inhibition zones were very similar: 37.0 and 36.0 mm pre- and postoperatively in study A (Table XVa) and 41.4 and 41.1 mm (Table XVb) respectively in study B. No statistically significant difference was recorded.

Bacteriological examination of the faecal flora:

In a first study comprising 9 patients undergoing TUR, the influence of a short cefotaxime course (1 g daily; 3-4 days) on the faecal aerobic Gram-negative flora was analysed according to the method described by Alestig and Lidin-Janson (1975). Rectal swabs were taken 1-3 days before the first intramuscular injection of cefotaxime and 7-10 days after the last dose (Table XVI a). Before the treatment, *Pseudomonas aeruginosa* was isolated from the faeces collected by rectal swabs in 4 patients and after treatment in 3 patients. No significant change was observed.

Table XVI a. Study on the influence of a short course with cefotaxime in conjunction with TUR on the *faecal coliform flora* (Alestig & Lidin-Janson, 1975). Resistance to cefotaxime is expressed according to the following score:

- 0 = No resistant strains of Enterobacteriaceae or Pseudomonas found
- 1 = Resistant strains of Enterobacteriaceae or Pseudomonas found but dominant strain probably sensitive.
- 2 = Dominant strain sensitive or resistant
- 3 = Dominant strain probably resistant
- x = Pseudomonas aeruginosa

Time of sampling	P a t i e n t s									mean score of resistance
	1	2	3	4	5	6	7	8	9	
1-3 days before the first cefotaxime dose	1 ^x	1 ^x	1 ^x	0	1 ^x	0	0	0	0	0.44
7-10 days after the last cefotaxime dose	0	1 ^x	2 ^x	0	1 ^x	0	0	0	0	0.44

Table XVI b. Study on the influence of a short course with cefotaxime in conjunction with TUR on the *faecal coliform flora*. Resistance to cefotaxime is expressed according to the same score as in Table XVI a.

Time of sampling	P a t i e n t s													mean score of resistance
	1	2	3	4	5	6	7	8	9	10	11	12	13	
1-3 days before the first cefotaxime dose	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 day after the last cefotaxime dose	2 ^x	0	0	1 ^x	0	0	0	0	0	1 ^x	0	0	0	0.31
7-10 days after the last cefotaxime dose	1 ^x	0	0	0	0	0	0	0	0	2 ^x	0	0	0	0.23

To specify whether any significant modification was detectable immediately after treatment, a second study was started. Rectal swabs were taken 1-3 days before the administration of the first cefotaxime dose, 1 day after the last dose and 7-10 days later (Table XVIB). None of the 13 patients investigated had resistant aerobic Gram-negative bacteria isolated before treatment. Immediately after the short cefotaxime course 3 patients displayed *Pseudomonas aeruginosa* and 2 in the 7-10 days examination. All these strains had MIC-values $\leq 16 \mu\text{g/ml}$. None of the analysis yielded any resistant Gram-negative species. The number of bacteria was not influenced by the antibiotic course.

The trial drug

The concentration of cefotaxime in serum (10 patients), urine (4) and prostate (15) were determined.

Concentration of cefotaxime:

A standard elimination curve representative for a group of elderly men was obtained. The mean serum peak was found at 60 minutes to be $24.9 \mu\text{g/ml}$ after injection of 1 g cefotaxime intramuscularly. The half life ($t_{1/2}$) was calculated to 84 minutes.

Cefotaxime concentration in urine:

The mean concentration at 2, 3, 5 and 24 hours were $3,395 \mu\text{g/ml}$, $3,107 \mu\text{g/ml}$, $1,210 \mu\text{g/ml}$ and $205 \mu\text{g/ml}$ respectively. Fifty per cent of the administered dose was found to be eliminated in the first three hours after injection and 87 per cent after 24 hours.

Cefotaxime concentration in prostate:

The mean concentration in the prostatic gland between 1-2 hours, 2-3 hours and > 3 hours were found to be 2.8, 2.4, $2.9 \mu\text{g/g}$ tissue. The ratio prostate - serum concentration of cefotaxime was calculated to 15 per cent in the first interval, 16 per cent in the second one and 31 per cent in the last observation period.

Tolerance and adverse reactions:

The drug was generally well tolerated. Pain was registered in the injection site in some patients.

No patients either in study A or study B showed any skin reaction or other clinical manifestation attributable to the drug.

No noteworthy modification of the liver enzymes was observed.

The *kidney function* was followed in study A by determination of serum creatinine and urea. All patients received the 'loop-diuretic' furosemide intravenously in doses between 80-120 mg generally. The patients in the antibiotic group thus received cefotaxime concomitant to furosemide. In both groups a slight elevation of serum creatinine and urea were recorded postoperatively within the first 48 hours. A return to the preoperatively normal range value was seen within one week after TUR, equal in both groups (Table XVII).

Table XVII. *Serum creatinine and urea (median) before and after TUR in the cefotaxime and the control groups, respectively.*

Group	S-creatinine		S-urea	
	Before	After	Before	After
Cefotaxime group	93 (n=34)	→ 107	5.9 (n=32)	→ 6.7
Control group	92 (n=42)	→ 106	6.4 (n=39)	→ 6.3

* Normal range: creatinine 60-115 µmol/l; urea 2-9 µmol/l.

Comments on results:

The importance of bacterial count in the diagnosis of urinary tract infection was stressed by Kass (1956). An arbitrary dividing line between bacteriuria and contamination was proposed at 10⁵ bacteria per ml (10⁸ CFU/L) or more. We presented the bacterial count in urine divided in two separate subgroups for several reasons. Firstly, lower bacterial count could be of clinical importance when the urine sample was aspirated from the catheter and in case of bladder incubation time less than 4 hours, as often occurred in newly operated patients. Secondly, forced diuresis was used peri- and postoperatively and the patients

were instructed to drink large quantities of liquid with subsequent dilution of the urine. Finally, we found Gram-negative urinary tract pathogens in the interval 10^7 - 10^8 CFU/L in a substantial number of patients, with or without symptoms. This suggests that a lower bacterial count (i.e. 10^7 - 10^8 CFU/L) should also be considered of clinical importance in many instances.

All diagnosed infectious complications were made on a *clinical basis* and required in addition the presence of bacteria in blood (septicemia) or urine (upper and lower urinary tract infection). Thus no presumptive diagnosis was accepted. No systematic blood culture was taken. Therefore the absolute frequency of bacteremia could not be determined and the frequency of septicemia might be underestimated.

All patients, even those who received antibiotics during the postoperative follow-up, are included in the presentation of the frequency of bacteriuria. Thus the figures also comprise the urine cultures that turned negative under or after treatment. As antibiotics more often were prescribed to the patients in the control group, the data give even more power to the intergroup difference in favour of the cefotaxime group.

Analysis of *bacterial isolates* regarding MIC-values was made at different periods for study A (1982), study B (spring 1983) and study C (fall 1983) which may explain the small differences. This was also the case of the size of the inhibition zones recorded on the initial urine culture (study A, 1978/1979); study B (1981).

DISCUSSION

Infectious complications following TUR are frequent and usually easy to treat, but may develop into life threatening conditions in elderly patients. These severe infectious complications occur within the first days or week after TUR. The sources could be related to the infected environment in which a majority of TUR are carried out. Firstly, the distal urethra is colonized with both Gram-negative and Gram-positive bacteria (Helmholz, 1955) which are known to enter the bladder through or beside the indwelling catheter (Kunin et al; Brehmer et al). The colonization of the meatus by potentially pathogenic bacteria is also shown to be a major risk factor for catheter-associated bacteriuria (Garibaldi et al). Secondly, recent works have confirmed the earlier stated fact that the prostate harbours pathogens (Evans, Gordon Smart & Bagshaw, 1981; Robinson, Arudpragasam, Sahgal, Cross, Akdas, Fittal & Sibbald, 1982). Evans et al, who studied deep prostatic layer after open surgery, found an increasing proportion of patients with bacterial growth within the specimen with prolonged period of catheterization. Thirdly, the prevalence of asymptomatic bacteriuria in men is known to increase with age (Freedman, 1983). The main cause of bacteriuria is described to be chronic prostatitis (Mears et al) but as suggested by Freedman (1983) it is likely that the changes in bladder function, prostate gland size, immunologic status and concomitant diseases also contribute to bacteriuria. Patients who are to undergo TUR are elderly men and almost all of them have been subjected to urological instrumentation. A substantial number of obstructions due to prostatic enlargement are diagnosed in conjunction with acute retention requiring treatment with indwelling catheter. With the intention of operating the patient in an apparent clean field, some authors have recommended to treat this group of patients before TUR with antibiotics (Genster et al; Landes et al; Mauermayer, 1981) and to prescribe an appropriate antimicrobial agent postoperatively in case of clinical signs of infection. Antibiotic prophylaxis during the operation has remained controversial (Chodak et al; Berger et al), advocated by some authors (Plorde et al; Hill et al; Morris et al; Gonzales et al) but refuted by others (Genster et al, Peters, 1979). Nevertheless keeping the earlier observations regarding the frequency of infectious complications and the sources of infection in mind, more knowledge concerning the value of antibiotics in TUR was considered important.

We conducted interventional studies with random allocation to an antibiotic group and to an untreated control group to evaluate the efficacy of antimicrobial agents. We opted for short antibiotic courses to minimize adverse reactions and resistance development. Another reason was that longer

antibiotic regimens had failed to prevent recurrence of bacteriuria (Genster et al; Christoffersen, Iversen, Jacobsen, Korner, Petersen, Rasmussen & Tybring, 1974). Furthermore Garibaldi et al (1974) showed that the preventive effect of antimicrobial agents declined after four days in catheterized patients. Therefore full efficacy could be expected during the first three days following TUR during which the patients carry an indwelling catheter. We primarily focused our attention on the frequency of bacteriuria, septicemia and upper urinary tract infections.

The perioperative timing in study A (I) (treatment initiated the day before the operation) was based on the observation that preoperatively bacteriuric patients run an increased risk of bacteremia and that the most favourable prophylactic results are obtained when adequate concentration of the antibiotic is achieved in serum and tissues exposed to the pathogen (Burke, 1961). The postoperative timing in study B (III) was chosen to investigate whether such a scheduled course could eliminate both persisting and postoperatively acquired bacteriuria. Furthermore it allowed us to follow the immediate postoperative succession of events regarding infections. The treatment was initiated just before the postoperative catheter was removed because this procedure may be followed by bacteremia and even septicemia (Richaud, 1976, p 36; Stamey, 1981, p 590; Cafferkey, 1982).

In our series of 192 and 96 patients respectively, 122 (42%) required bladder drainage with an indwelling catheter usually for several weeks prior to TUR and 92 per cent of these catheterized patients had bacteriuria. Fifteen per cent of the non-catheterized patients also had bacteriuria with few or no symptoms. The frequency of bacteriuria ranging from 40 to 63 per cent in the different groups confirmed the infected environment in which TUR was carried out.

Considering *all patients*, the short perioperative antibiotic course (study A) significantly reduced the frequency of postoperative bacteriuria compared to the preoperative one. This observation is remarkably different from the unchanged proportions observed in both the control groups in both studies and the group receiving the antibiotic postoperatively (study B). These data demonstrate the superiority of a perioperative antibiotic course to a postoperatively timed one.

Two groups of patients have to be considered separately: a) the preoperatively non-bacteriuric patients in whom the antimicrobial agent exerts a pure prophylactic effect; b) the preoperatively bacteriuric patients in whom the

antibacterial agent acts therapeutically.

Preoperatively non-bacteriuric patients receiving no antibiotics acquire bacteriuria in high percentage (Table II). Our trials confirm this observation which also gains further support in numerous recent studies (Table XVIII). Usually these patients do well, half of them curing spontaneously, the other half requiring antibiotics. Nevertheless postoperatively acquired bacteriuria may lead in some cases to severe infectious complications. Four out of 52 (8%) preoperatively non-bacteriuric patients in the control group developed upper urinary tract infection (study A). This is consistent with a recent publication by Murphy et al (1983) who reported that 5 out of 18 cases of septicemia in 1,604 patients undergoing TUR occurred in preoperatively non-bacteriuric patients. In contrast no significant bacteriuria and no infectious complications were recorded among the patients receiving cefotaxime perioperatively (study A). Also in study B, no serious events followed TUR in the antibiotic group among the preoperatively non-bacteriuric patients.

We conclude from these results that the *prophylactic effect* of a perioperative antimicrobial agent is undisputable and to prefer to no treatment at all, because untreated patients will require antibiotic prescription postoperatively in a substantial number of cases and because there is an existing risk of a severe infectious complication in terms of upper urinary tract infection and septicemia.

Almost all patients with *bacteriuria before TUR* and receiving no antibiotics remain with infected urine postoperatively for a long time (Plorde et al, Genster et al). Our studies confirm this observation (control groups, both studies) and only in a few cases (less than 10 per cent) the operation per se and the subsequent amelioration of micturition cured the patients from bacteriuria. Thus most patients remained with untreated asymptomatic bacteriuria or received antibacterial agents for symptomatic urinary tract infection. In contrast cefotaxime in a short perioperative course eliminated bacteriuria postoperatively in approximately 2/3 of the patients (study A) while the postoperatively scheduled course showed no such favourable results (study B). Bacteriuric patients at the time of TUR are known to be at risk of bacteremia and septicemia (Table III and IV). This was also confirmed in our trials (study A and B) in which all five cases of septicemia occurred in bacteriuric patients not covered by an antibiotic. Nine out of 13 cases of upper urinary tract infections also occurred in preoperatively bacteriuric patients. On the other hand when the antibiotic was given perioperatively, no such cases were recorded at all.

The immediate postoperative difference in the outcome of both severe infectious

Table XVIII. Frequency of *acquired bacteriuria* after TUR in patients with perioperative antibiotic course or without. Prophylactic effect. Clinical trials 1979-1983.

Author	Antimicrobial agent & (schedule)*	With antimicrobial agent		Without antimicrobial agent		p value
		No patients investigated	Acquired bacteriuria (per cent)	No patients investigated	Acquired bacteriuria (per cent)	
Peters (1979)	different	86	59	110	53	N.S.
Nielsen et al (1981)	cefoxitin (cath. rem.)	49	6	50	42	p<0.001
Williams et al (1980)	cephradine (48 h)	59	12	76	43	p<0.001
Hargreave et al (1982)	cefotaxime (48 h)	120	10	119	26	p<0.01
Iversen et al (1982)	cefotaxime (at operat.)	37	8	-	-	-
	cefazolin (24 h)	37	5	-	-	-
	cefotaxime (24 h)	38	5	-	-	-
Holl et al (1982)	nitrofurantoin (10 d) co-trimoxazole	60	10	40	20	N.S.
Ramsey et al (1983)	gentamicin (12 h)	18	22	20	45	N.S.
	gentamicin (5 days)	15	20			N.S.
	gentamicin (1 dose)	19	11			p<0.02
Goldwasser et al (1983)	co-trimazole (10 d)	26	4	25	32	p<0.01
	co-trimazole (2 doses)	26	4			
Falkiner et al (1983)	cephradine + nitrofurantoin (5 d)	20	10	24	62	p<0.01
	nitrofurantoin (5 d)	29	7	31	48	p<0.01

* The following abbreviations are used: cath. rem.=treatment given to cover the period to catheter removal; at operat.= treatment given at operation; 24/48 h.= treatment given for 24 or 48 hours; d=days.

complications and the frequency of bacteriuria between both studies clearly indicates that perioperatively scheduled antibiotic courses are superior to postoperatively timed ones.

We conclude from these observations that in *bacteriuric patients* antimicrobial agents are of great advantage by protecting against severe postoperative infectious complications and by significantly reducing the frequency of postoperative bacteriuria.

All severe infectious complications were caused by Gram-negative pathogens. Consequently it is essential to focus primarily on Gram-negative bacteria in the rational choice of an antimicrobial agent to be used in conjunction with transurethral surgery.

A slight elevation of the *body temperature* is regularly seen after TUR and is discussed by many authors referred to in this review. Most of them describe no significant influence of antibiotics on the postoperative body temperature. Our recordings confirm this statement and indicate that a slight elevation of the temperature is a normal reaction to the operation.

The *recurrence* and *persistence* of bacteriuria were studied. In most cases the same strain recurred (cefotaxime group) or persisted (control group), as determined by the sensitivity pattern and for *E. coli* by determination of the serotype. All recurring and persisting isolated strains in study A and B were sensitive to cefotaxime except for some enterococci and in all cases of recurrence or persistence of bacteriuria, a clinical reason could be found. In most cases the cause was preoperative treatment with urethral indwelling catheter. Other predisposing factors were chronic prostatitis (determined by histopathologic examination), chronic pyelonephritis scars or prostatic cancer with obstruction of the upper urinary tract. This observation indicates that indwelling catheters favours infections in the lower urinary tract including the prostatic gland and predisposes to chronic bacteriuria.

Hargreave et al (1982) demonstrated a significant reduction of the period of hospitalization in a group of patients receiving a 48-hour course of cefotaxime in conjunction with TUR compared to a control group. The mean stay in hospital differed by one day. The same difference was found by Goldwasser et al (1983) although no statistically significant difference was found in this smaller material. Nielsen et al (1981) also showed almost a one day (0.8 day) reduction in the postoperative hospital stay, using cefoxitin vs placebo.

In study A, the same trend was recorded. The patients in the cefotaxime group were hospitalized a slightly shorter period (difference of mean hospital stay: 0.8 day) compared to the controls. The difference was not statistically significant. The severe infectious complications observed in the control group could partly explain this longer period. Nearly one day of intergroup difference may not be regarded as important, but keeping the large number of men who are to undergo TUR in mind, the economic advantages of a short antibiotic course are to be considered.

Neither cancer of the prostate nor the preoperative treatment with an indwelling catheter significantly influenced the period of hospitalization although these two groups of patients were hospitalized for a slightly longer period compared to patients with benign hyperplasia and patients not carrying a catheter prior to TUR, respectively. The greater difference observed in study B (1.6 days) can be explained on the one hand by the higher number of patients within the control group with postoperative severe infectious complications, cancer of the prostate and preoperative treatment with an indwelling catheter and on the other hand by the intergroup age difference. Indeed, the patients under 70 years were discharged from hospital significantly shorter a period after TUR compared to patients 70 years and above.

The patients in trial A were followed and retrospectively reviewed 3 to 4 years (mean 3.5 years) after TUR to investigate whether a short perioperative antibiotic course had any impact on the long term mortality and morbidity. We focused on survival rate, infectious events and potentially related long-term complications and the patients' appraisal of the results of the operation. Late mortality, evenly distributed between the groups, was not influenced by the perioperative course, and could be ascribed to either cardiovascular or malignant diseases, mainly cancer of the prostate or of the gastro-intestinal tract. Regarding late morbidity there was a predominance of infectious events among the controls. Two patients undergoing renewed endoscopic operation and not covered by antibiotics, developed severe infectious complications. This observation underlines once more the important role of antimicrobial agents in such procedures, at least in bacteriuric patients. Bacteriuria was diagnosed in 24 per cent of the patients at late follow-up after TUR confirming the high prevalence of bacteriuria in elderly men, even after amelioration of micturition and the patients' positive view on the results of the operation. Furthermore 12 instances of stricture of the urethra or the bladder neck were observed (IV), 10 of them in the control group. After exclusion of the 4 soft meatal strictures, an intergroup difference was recorded ($p=0.05$) suggesting an interrelationship between stricture formation and infectious events,

although no causal factor such as bacteriuria could be pointed out. Eighty-three per cent of the patients were satisfied with the results of the operation on the reckoning on average 3.5 years after TUR. Nevertheless 41 per cent complained of symptoms from the lower urinary tract, mainly in terms of frequency and painful voiding. Neither bacteriuria nor symptoms from the lower urinary tract could be related to reduced urinary flow. The favourable results shown by this follow-up study (IV) are consistent with the reports by others regarding TUR (Lund et al; Chilton et al). The study also points out the importance of infectious events in conjunction with renewed endoscopic procedures, the prevalence of bacteriuria in elderly men after prostatectomy and the difficulty in eliminating bacteriuria in some patients by means of antimicrobial agents. Finally the data suggest further long-term follow-up of patients undergoing TUR with or without antibiotic to gather more information on the cause-effect relation of stricture formation.

Cefotaxime was found in therapeutically adequate concentration in serum, urine and tissues of urological patients including kidney and prostate. We also found that cefotaxime was well tolerated during the trials, caused no toxicity or adverse reactions and did not influence the renal function even when administered concomitantly with furosemide. A high antimicrobial activity was seen. Thus cefotaxime was found to be a safe antimicrobial agent when used in a short perioperative course in conjunction with TUR and under controlled conditions.

One of the principal objections to antibiotic prophylaxis is the risk of development of resistant bacteria. Indeed, antimicrobial agents profoundly influence the gut flora (Winberg, Bergström, Lincoln & Lidin-Janson, 1973) which is an important reservoir for urinary tract pathogens (Turck, Petersdorf & Fournier, 1962). After 10 days of treatment with doxycycline and tetracycline isolated *E. coli* strains are resistant to the drugs in 80 and 100 per cent respectively (Alestig & Lidin-Janson, 1975). A similar selective pressure is demonstrated for sulphonamides (Lidin-Janson, 1977) and to a lower rate for amoxycillin and cephradine (Lacey, Hawson, Lord, Luxton & Trotter, 1983) and cephalosporins used parenterally and orally as prophylaxis in heart surgery (Lucain, Duceł & Piffaretti, 1982). Furthermore 'problem' pathogens such as highly resistant *Serratia marcescens* or *Pseudomonas aeruginosa* organisms have emerged when prophylactic antibiotic courses were used in conjunction with TUR (Gibbons et al; Peters, 1979).

Our investigations on the faecal flora were carried out to analyse whether

short courses also exerted a selective pressure on the aerobic Gram-negative strains. In our patients subjected to TUR and receiving cefotaxime for 3 to 4 days, no significant influence on the coliform strains could be observed. None of the analyses yielded any resistant coliform species or *Candida*. Consequently this observation is in opposition to the studies mentioned above in which the antimicrobial agents were given for a longer time than one week and high frequencies of resistant strains emerged.

We also critically analysed the impact of short antibiotic courses on the bacterial environment in patients subjected to TUR after more than five years of utilization of cefotaxime in our department. During this period of time the drug was used on the one hand in short-term courses in TUR and on the other hand in severe urinary tract infections including systemic involvement (septicemia) not caused by TUR. We compared the preoperatively isolated bacteria from patients in study A, B and C. The distribution of species was similar throughout the whole period. The bacterial isolates acquired in the hospital environment did not differ noticeably regarding neither the sensitivity pattern nor the distribution. The MIC-values for each species remained unchanged as were the geometric means of the MIC-values of all strains except for enterococci, a bacteria known to be resistant to cephalosporins.

The isolated species showed to be sensitive to drugs such as cefotaxime, gentamicin, co-trimazine and the combination of ampicillin and mecillinam, but to have reduced sensitivity to commonly used drugs such as ampicillin, nitrofurantoin and nalidixic acid.

The high in vitro activity of cefotaxime against most strains in our studies is similar to the results obtained in the same hospital from 662 different clinical isolates (Forsgren, 1981) and from 523 blood culture isolates (Ode, Forsgren & Walder, 1983).

The results concerning the microbial environment lead us to the conclusion that well-adjusted short-term scheduled antimicrobial courses given in conjunction with TUR are harmless from an ecological point of view. However, to avoid unexpected and undesirable environment problems, a permanent epidemiological surveillance of the common pathogens found in the community is fundamental. This can be achieved by a continuous recording or by an intermittent assessment of the isolates looking for changes in distribution and sensitivity. Such a surveillance is the guide to the choice of suitable drugs to be used for prophylaxis and treatment, respectively.

CONCLUSIONS

1. A short course with a potent antibiotic (cefotaxime) given to patients subjected to TUR:
 - a) reduces significantly the frequency of postoperative bacteriuria when given *perioperatively* (I) but not *postoperatively* (III)
 - by protecting preoperatively non-bacteriuric patients from developing bacteriuria
 - by eliminating bacteriuria in more than half of the preoperatively bacteriuric patients.
 - b) protects against severe infectious complications in the early postoperative period when given *perioperatively* (I) but not *postoperatively* (III).
2. A short *perioperative* course with cefotaxime did not influence long-term mortality but was associated with a lower frequency of infectious events and subsequent prescription of antibiotics and also a significant lower frequency of postoperative stricture formation compared to an untreated control group (IV).
3. *Gram-negative* bacteria predominated over Gram-positive bacteria (70-80 % vs 20-30 %) in patients undergoing TUR. Isolated bacteria were found to be sensitive to such antibiotics as cefotaxime, gentamicin, trimethoprim, co-trimazine and the combination of ampicillin and mecillinam, but to have a reduced sensitivity to drugs such as ampicillin, cephalexin, nalidixic acid and nitrofurantoin (II) (III).

In spite of *in vitro* sensitivity to cefotaxime, *recurrence* of bacteriuria occurred after TUR and could be explained by preoperative treatment with indwelling catheter, chronic prostatitis, chronic pyelonephritis or cancer of the prostate. The same diagnosis caused *persistence* of bacteriuria in untreated patients (II)(III).
4. No change of the *species distribution* or *sensitivity pattern* was observed among bacteria isolated from patients subjected to TUR during more than five years of use of cefotaxime. No significant influence on the faecal flora was observed in patients receiving a short course of cefotaxime.
5. Cefotaxime was found in therapeutically adequate concentrations in serum, urine and prostate (V). No adverse reactions were observed during the trials (I)(III).

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to

Lars B. Wadström, my chief, who led me into the field of Urology, for generous support.

Sverker Hellsten, my friend and supervisor, who stimulated my interest in clinical research and who with never-failing enthusiasm, supported the work. I thank him for fruitful discussions and constructive criticism.

Arne Forsgren, who introduced me into the field of medical microbiology, for his friendly guidance and generous support, his positivism and expert criticism.

The staff of the urological wards for faithful care of the patients, smooth running of the clinical trials and accurate collection of clinical data.

Ingrid Persson and her co-workers at the department of medical microbiology, for careful and devoted work with the bacteriological investigations and sensitivity tests. I thank *Ann-Christin Fredin* for excellent work with the determination of drug concentration.

My colleagues and friends from the Department of Urology, who treated most of the patients, for stimulating discussions and assistance.

Karl-Erik Andersson for interest and stimulating discussions on pharmacokinetic issues and for chemical analysis of the drug.

The secretarial staff of the Department of Urology for continuous assistance with the extensive secretarial work. I thank *Ann Cathrin Werther* for devoted handling of medical records and *Christina Gullstrand* for invaluable help with contact with the patients and collection of data.

Marleen Andersson for performing excellent secretarial work and typing of manuscripts and *Maj Nilsson* for competent and patient typing of this and other manuscripts.

Finally, I want to express my gratitude to my *father* and my *late mother* for never-failing support throughout my education.

Permission to include paper V was granted by MMV Medizin Verlag, München.

REFERENCES

- Alcock, N.G. 1932. Ten months experience with transurethral prostatic resection. *J Urol*, 28, 545-559.
- Alestig, K & Lidin-Janson G. 1975. The effect of Doxycycline and Tetracycline Hydrochloride on the aerobic fecal flora. *Scand J Infect Dis* 7, 265-271.
- Altenmeier, W.A., Todd, J.C. & Wellford W.I. 1967. Gram-negative septicemia: A growing threat. *Ann Surg*, 166, 530-541.
- Argyrou, S., Blandy, J.P., Gow, J.G., Singh, M., Tresidder, G.C. & Vinnicombe, J. 1974. Price of prostatectomy. *Br Med J*, 3, 511-513.
- Bandhauer, K. & Madersbacher, H. 1969. Früh- und Spätkomplikationen transurethraler Eingriffe an der Prostata. *Der Urologe*, 8. Jahrgang, Heft 2, 49 - 57.
- Bandhauer, K., Grob, H.U., Keller, U. & Kreutz, G. 1977. Die transurethrale Prostataektomie - ein Ausbildungsproblem. *Aktuelle urologie* 8, 173 - 179.
- Barrington, F.J.F & Wright, H.D. 1930. Bacteraemia following operations on the urethra. *J Path Bact*, 33, 871 - 885.
- Bastable, J.R.G., Peel, R.N., Birch, D.M. & Richards, B. 1977. Continuous irrigation of the bladder after prostatectomy: Its effect on post-prostatectomy infection. *Br J Urol*, 49, 689-693.
- Berger, S.A. & Nagar, H. 1978. Antimicrobial prophylaxis in urology. *J Urol*, 120, 319 - 322.
- Bergman, R.T., Turner, R, Barnes, R.W. & Hadley, H.L. 1955. Comparative analysis of one thousand consecutive cases of transurethral prostatic resection. *J Urol*, 74, 533-545.
- Biorn, C.L., Browning, W.H. & Thompson, L. 1950. Transient bacteremia immediately following transurethral prostatic resection. *J Urol*, 63, 155-161.
- Brehmer, B & Madsen, P.O. 1972. Route and prophylaxis of ascending bladder infection in male patients with indwelling catheters. *J Urol*, 108, 719 - 721.
- Br Med J*, 1, 634, 1975. News and notes: Epidemiology, bacteraemia.
- Britt, M.R., Burke, J.P., Miller, W.A., Steinmüller, P. & Garibaldi, R.A. 1976. The non-effectiveness of daily meatal care in the prevention of catheter-associated bacteriuria. 16th Interscience Conference on antimicrobial agents and chemotherapy, Chicago, U.S.A.
- Burke, J.F. 1961. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*, 50, 161-168.
- Butler, H.K. & Kunin, C.M. 1968. Evaluation of polymyxin catheter lubricant and impregnated catheters. *J Urol*, 100, 560 - 566.
- Cafferkey, M.T., Conneely, B., Falkiner, F.R., Gillespie, W.A. & Murphy, D. 1980. Post-operative urinary infection and septicaemia in urology. *J Hosp Inf*, 1, 315 - 320.
- Cafferkey, M.T., Falkiner, F.R., Gillespie, W.A. & Murphy, D.M. 1982. Antibiotics for the prevention of septicaemia in urology. *J Antimicrob Chemother*, 9, 471-477.

- Cass, A.S. 1969. Transurethral prostatic resection without catheter drainage. *J Urol*, 101, 750 - 751.
- Chilton, C.P., Morgan, R.J., England, H.R., Paris, A.M.I. & Blandy, J.P. 1978. A critical evaluation of the results of transurethral resection of the prostate. *Br J Urol*, 50, 542-546.
- Chodak, G.W. & Plaut, M.E. 1979. Systemic antibiotics for prophylaxis in urologic surgery: A critical review. *J Urol*, 121, 695-699.
- Christoffersen, J.C., Iversen, H.-G., Jacobsen, J., Korner, B., Petersen, H.K. Rasmussen, F. & Tybring, L. 1974. Fl 1039 in bacteriuria following prostatectomy. *Scand J Urol Nephrol*, 8, 185-192.
- Clark, A. 1883. Remarks on catheter fever. *The Lancet*, Dec 22, 1883, 1075 - 1077.
- Collste, L.G. & Törnqvist, H. 1978. Urinary infection and transurethral prostatectomy. *Scand J Urol Nephrol*, 12, 7-9.
- Colton, T. 1974. *Statistics in medicine*. Little, Brown and Company, Boston, First Edition.
- Cowan, S.T. & Steel, K.J. *Manual for the identification of medical bacteria*, Cambridge University Press, London, 1970.
- Creevy, C.D. 1951. The mortality of transurethral prostatic resection. *J Urol*, 65, 876-882.
- Creevy, C.D. & Feeney, M.J. 1954. Routine use of antibiotics in transurethral prostatic resection: A clinical investigation. *J Urol*, 71, 615-623.
- Danielsson, D. 1978. Infections of the male genital tract. *Intern J Androl*, Supp 1, p. 43.
- Davis, T.M. 1931. Prostate operation: Prospects of the patients with prostatic disease in prostatectomy vs. resection. *J.A.M.A.*, 97, 1675-1679.
- Desautels, R.E. 1960. Aseptic management of catheter drainage. *New Engl J Med*, 263, 189-191.
- DuPont, H.L. & Spink, W.W. 1969. Infections due to Gram-negative organisms: An analysis of 860 patients with bacteremia at the university of Minnesota Medical Center. *Med*, 48, 307-332.
- Ericsson, H.M. & Sherris, J.C. 1971. Antibiotic sensitivity testing. Report of an international collaborative study. *Acta Path Microbiol Scan (B)*, Suppl, No 217.
- Essenhigh, D.M. & Eustace, B.R. 1969. The use of frusemide (Lasix) in the post-operative management of prostatectomy. *Br J Urol*, 41, 579-585.
- Evans, J.P., Smart, J.G. & Bagshaw, P.F. 1981. Bacterial content of enucleated prostate glands. *Urol*, XVII (4), 328 - 331.
- Falkiner, F.R., Ma, P.T.S., Murphy, D.M., Cafferkey, M.T. & Gillespie, W.A. 1983. Antimicrobial agents for the prevention of urinary tract infection in transurethral surgery. *J Urol*, 129, 766-768.

Felty, A.R. & Keefer, C.S. 1924. *Bacillus coli* sepsis: A clinical study of twenty-eight cases of blood stream infection by the colon bacillus. *J.A.M.A.* 82, 1430-1433.

Forsgren, A. 1981. Comparative in vitro activity of first, second and third generation cephalosporins. *Acta Path Microbiol Scan (B)*, 89, 221-225.

Fraser, I., MacPherson, S. & Panagakis, A. 1978. Should patients be shaved prior to transurethral surgery? *Br J Urol*, 50, 109-110.

Freedman, L.R. 1983. Urinary-tract infections in the elderly. *New Engl J Med*, 309, 1451-1452.

Freedman, R. & Berelson, B. 1974. The human population. *Sc. Am.*, 231, 31-39.

Garibaldi, R.A., Burke, J.P., Dickman, M.L. & Smith, C.B. 1974. Factors predisposing to bacteriuria during indwelling urethral catheterization. *N Engl J Med*, 291, 215-219.

Garibaldi, R.A., Burke, J.P., Britt, M.R., Miller, W.A. & Smith, C.B. 1980. Meatal colonization and catheter-associated bacteriuria. *N Engl J Med*, 303, 316-318.

Gaudin, H.J., Zide, H.A. & Thompson, G.J. 1938. Use of sulfanilamide after transurethral prostatectomy. *J.A.M.A.*, 110, 1887-1890.

Genster, H.G. & Madsen, P.O. 1970. Urinary tract infections following transurethral prostatectomy: With special reference to the use of antimicrobials. *J Urol*, 104, 163-168.

Gibbons, R.P., Stark, R.A., Correa, Roy J, Cummings, K.B. & Mason, J.T. 1978. The prophylactic use-or misuse- of antibiotics in transurethral prostatectomy. *J Urol*, 119, 381-383.

Goldwasser, B., Bogokowsky, B., Nativ, O., Sidi, A.A., Jonas, P & Many, M. 1983. Prophylactic antimicrobial treatment in transurethral prostatectomy. *Urol*, XXII (2), 136-138.

Gonzales, R., Wright, R. & Blackard, C.E. 1976. Prophylactic antibiotics in transurethral prostatectomy. *J Urol*, 116, 203-205.

Guze, L.B. & Beeson, P.B. 1956. Observations on the reliability and safety of bladder catheterization for bacteriologic study of the urine. *N Engl J Med*, 255, 474.

Hamilton-Miller, J.M.T., Brumfitt, W. & Reynolds, A.V. 1978. Cefotaxime (HR 756) a new cephalosporin with exceptional broad spectrum activity in vitro. *J Antimicrob Chemother*, 4, 437-444.

Hargreave, T.B., Hindmarsh, J.R., Elton, R., Chisholm, G.D. & Gould, J.C. 1982. Short-term prophylaxis with cefotaxime for prostatic surgery. *Br Med J*, 284, 1008-1010.

Hart, A.J.L. & Fowler, J.W. 1981. Incidence of urethral stricture after transurethral resection of prostate. *Urol*, XVIII (6), 588-591.

Helmholz, H.F. 1950. Determination of the bacterial content of the urethra: A new method, with results of a study of 82 men. *J Urol*, 64(1), 158-166.

Hills, N.H., Bultitude, M.I. & Eykyn, S. 1976. Co-trimoxazole in prevention of bacteriuria after prostatectomy. *Br Med J*, 2, 498-499.

- Hofstetter, A., Schilling, A & Marx, F.J. 1977. Urosepsis bis septischer Schock III. Mikrobiologische Probleme. Urologe A 16, 346-350.
- Holl, W.H. & Rous, S.N. 1982. Is antibiotic prophylaxis worthwhile in patients with transurethral resection of prostate? Urol, XIX(1), 43-46.
- Holtgrewe, H.L. & Valk, W.L. 1962. Factors influencing the mortality and morbidity of transurethral prostatectomy: A study of 2,015 cases. J Urol, 87, 450-459.
- Holtgrewe, H.L. & Valk, W.L. 1964. Late results of transurethral prostatectomy. J Urol, 92, 51-55.
- Hunt, V.C. & Walters, W.A. 1938. Suprapubic prostatectomy: Report on one thousand cases. Surg. gynec & Obst., 46, 769.
- Iversen, P. & Madsen, P.O. 1982. Short-term cephalosporin prophylaxis in transurethral surgery. Clin Therap 5 (Suppl A).
- Jackaman, F.R. & Chisholm, G.D. 1975. Urinary infection and prostatectomy. Br J Urol, 47, 545 - 548.
- Jacob, L. 1909. Über Allgemeininfektion durch *Bacterium coli commune*, Dtsch Arch klin Med, 97, 303-347.
- Juhlin, I. & Ericsson, C. 1961. A new medium for bacteriological examination of stools (LSU-Agar). Acta Path Microbiol Scan, 52, 185-199.
- Kass, E.H. 1956. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians, 69, 56-64.
- Kidd, E.E. & Burnside, K. 1965. Bacteraemia, septicaemia and intravascular haemolysis during transurethral resection of the prostate gland. Br J Urol, 37, 551 - 559.
- Kreger, B.E., Craven, D.E. & McCabe, W.R. 1980. Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med, 68, 344 - 355.
- Kunin, C.M. & McCormack, R.C. 1966. Prevention of catheter-induced urinary-tract infections by sterile closed drainage. N Engl J Med, 274, 1155 - 1161.
- Kunin, C.M. & Finkelberg, Z. 1971. Evaluation of an intraurethral lubricating catheter in prevention in catheter-induced urinary tract infections. J Urol, 106, 928 - 930.
- Lacey, R.W., Howson, G.L., Lord, V.L., Luxton, D.E.A. & Trotter, I.S. 1983. Double-blind study to compare the selection of antibiotic resistance by amoxycillin or cephadrine in the commensal flora. Lancet, 2, 529 - 532.
- Landes, R.R., Medenbach, K. & Lee, R.E. 1976. Effect of preoperative antibiotic therapy on bacterial prostatitis after transurethral prostatectomy. Urol, VIII (4), 352 - 356.
- Lentz, Jr., H.C., Mebust, W.K., Foret, J.D. & Melchior, J. 1977. Urethral strictures following transurethral prostatectomy: Review of 2,223 resections. J Urol, 117, 194 - 196.
- Lidin-Janson, G. 1977. Sulphonamides in the treatment of acute *escherichia coli* infection of the urinary tract in women. Scand J Infect Dis, 9, 211 - 217.

Lucain, C., Ducel, G. & Piffaretti, J.-C. 1982. Evolution de flores intestinales de patients traités à titre prophylactique par des céphalosporines. Schweiz med Wschr, 112, 817 - 823.

Lund, B.-L. & Dingsør, E. 1976. Benign obstructive prostatic enlargement. Scand J Urol Nephrol, 10, 33 - 38.

Lytton, B., Emery, J.M. & Harvard B.M. 1968. The incidence of benign prostatic obstruction. J Urol, 99, 639 - 645.

Madersbacher, H. & Marberger, H. 1971. Zur Harnröhrenstriktur nach transurethralen Operationen. Der Urologe (A), 10. Jahrgang, Heft 2, 66 - 67.

Matthew, A.D., Gonzales, R., Jeffords, D. & Pinto, M.H. 1978. Prevention of bacteriuria after transurethral prostatectomy with nitrofurantoin macrocrystals. J Urol, 120, 442 - 443.

Mauermayer, W. 1981. Transurethrale Operationen. Springer-Verlag, Berlin, Heidelberg, New York.

McCabe, W.R. & Jackson, G.G. 1962. Gram-negative bacteremia. I. Etiology and ecology. Arch Int Med, 110, 847 - 855.

McCarthy, J.F. 1931. A new apparatus for endoscopic plastic surgery of the prostate, diathermia and excision of vesical growths. J Urol, 26, 695 - 696.

McGuire, E.J. 1974. Antibacterial prophylaxis in prostatectomy patients. J Urol, 111, 794 - 798.

McKelvie, G.B. 1962. Intravenous urea as a diuretic in prostatectomy. Br Med J, 2, 1711 - 1717.

McLaughlin, W.L., Bowler, J.P. & Holyoke, J.B. 1948. The causes of death following transurethral resection of the prostate. J Urol, 59, 1233 - 1238.

Mears, E.M. & Stamey, T.A. 1972. The diagnosis and management of bacterial prostatitis. Br J Urol, 44, 175 - 179.

Melchior, J., Valk, W.L., Foret, J.D. & Mebust, W.K. 1974. Transurethral prostatectomy: Computerized analysis. J Urol, 112, 634 - 642.

Merritt, W.A. 1951. Bacterial endocarditis as a complication of transurethral prostatic resection. J Urol, 65, 100 - 107.

Mitchell, J.P., Slade, N. & Linton, K.B. 1962. Instrumental bacteraemia and its prevention. Br J Urol, 34, 454 - 458.

Morris, M.J., Golovsky, D., Guinness, M.D.G. & Maher, P.O. 1976. The value of prophylactic antibiotics in transurethral prostatic resection: a controlled trial, with observations on the origin of postoperative infection. Br J Urol, 48, 479 - 484.

Murphy, D.M., Falkiner, F.R., Carr, M., Cafferkey, M.T. & Gillespie, W.A. 1983. Septicemia after transurethral prostatectomy. Urol, XXII (2), 133 - 135.

Nielsen, O.S., Maigaard, S., Frimodt-Møller, N. & Madsen, P.O. 1981. Prophylactic antibiotics in transurethral prostatectomy. J Urol, 126, 60 - 62.

Obrant, K.O. 1976. Transurethral electroresection of prostatic adenoma. Scand J Urol Nephrol, 10, 26 - 32.

- O'Flynn, J.D. 1967. Prostatectomy - A review of 3,083 cases. J Irish Med Assoc, LX, 311 - 318.
- Ode, B., Forsgren, A. & Walder, M. 1983. Sensitivity of 523 blood culture isolates to 33 antibiotics. Scand J Infect Dis, in press.
- Peters, H.-J. 1979. Antibiotische Prophylaxe nach urologischen Operationen. Dtsch med Wschr, 104, 347 - 352.
- Plorde, J.J., Kennedy, R.P., Bourne, H.H., Ansell, J.S. & Petersdorf, R.G. 1965. Course and prognosis of prostatectomy. With a note on the incidence of bacteremia and effectiveness of chemoprophylaxis. N Engl J Med, 272, 269 - 277.
- Quintiliani, R., Cunha, B.A., Klimek, J. & Maderazo, E.G. 1978. Bacteraemia after manipulation of the urinary tract. The importance of pre-existing urinary tract disease and compromised host defence. Postgr med J, 54, 668 - 671.
- Ramsey, E. & Sheth, N.K. 1983. Antibiotic prophylaxis in patients undergoing prostatectomy. Urol, XXI(4), 376 - 378.
- Richaud, C. 1976. Les septicémies en urologie. J Urol Nephrol, 82, Suppl 1, 34 - 36.
- Robinson, H.P. & Greene, L.F. 1962. Postoperative contracture of the vesical neck. I. Review of cases and proposed theory of etiology. J Urol, 87, 601 - 608.
- Robinson, M.R.G., Cross, R.J., Shetty, M.B. & Fittall, B. 1980. Bacteraemia and bacteriogenic shock in district hospital urological practice. Br J Urol, 52, 10 - 14.
- Robinson, M.R.G., Arudpragasam, S.T., Sahgal, S.M., Cross, R.J., Akdas, A. Fittal, B & Sibbald, R. 1982. Bacteraemia resulting from prostatic surgery: the source of bacteria. Br J Urol, 54, 542 - 546.
- Rutishauser, G., Schubarth, P., Graber, P., Baumann, J. & Leibundgut, B. 1974. Welche Risiken hat die "Prostatektomie" heute? Schweiz med Wschr, 104, 10 - 15.
- Sach, R & Marshall, V.R. 1977. Prostatectomy: its safety in an Australian teaching hospital. Br J Surg, 64, 210 - 214.
- Scott, W.W. 1929. Blood stream infections in urology. A report of eighty-two cases. J Urol XXI(5), 527 - 566.
- Siegel, S. 1956. Non-parametric statistics for the behavioral sciences. McGraw-Hill - Kogakusha Ltd, Intern Student edition.
- Singh, M., Tresidder, G.C. & Blandy, J.P. 1973. The evaluation of transurethral resection for benign enlargement of the prostate. Br J Urol, 45, 93 - 102.
- Slade, N. 1958. Bacteraemia and septicemia after urological operations. Proc Roy Soc Med, 51, 331 - 334.
- Stamey, T.A. 1980. Pathogenesis and treatment of urinary tract infections. Williams & Wilkins, Baltimore/London.
- Stern, M. 1926. Resection of obstructions at the vesical orifice. J.A.M.A., 87, 1726 - 1730.

- Sullivan, N.M., Sutter, V.L., Mims, M.M., Marsh, V.H. & Finegold, S.M. 1973. Clinical Aspects of bacteremia after manipulation of the genitourinary tract. *J Inf Dis*, 127(1), 49 - 55.
- Swedish reference group for antibiotics. A revised system for antibiotic sensitivity. *Scan J Inf Dis*, 13, 148-152. 1981.
- Svanbom, M. 1979. Septicemia I. A prospective study on etiology, underlying factors and sources of infection. *Scand J Infect Dis*, 11, 187 - 198.
- Symes, J.M., Hardy, D.G., Sutherns, K. & Blandy, J.P. 1972. Factors reducing the rate of infection after trans-urethral surgery. *Br J Urol*, 44, 582 - 586.
- Thompson, G.J. 1951. Twenty-five years' experience with transurethral prostatic resection. *Surg Clin N Am*, Aug, 875 - 885.
- Turck, M., Petersdorf, R.G. & Fournier, M.R. 1962. The epidemiology of non-enteric *Escherichia coli* infections: prevalence of serological groups. *J Clin Invest*, 41, 1760 - 1765.
- Waisbren, B.A. 1951. Bacteremia due to Gram-negative bacilli other than the salmonella. *Arch Int Med*, 88, 467 - 483.
- Warren, J.W., Platt, R. Thomas, R.J., Rosner, B. & Kass, E.H. 1978. Antibiotic irrigation and catheter-associated urinary-tract infections. *N Engl J Med*, 299, 570 - 573.
- Wear, Jr., J.B. & Haley, P. 1973. Transurethral prostatectomy without antibiotics. *J Urol*, 110, 436 - 440.
- Webb, J.K. & Blandy, J.P. 1968. Closed urinary drainage into plastic bags containing antiseptic. *Br J Urol*, 40, 585 - 588.
- Westoff, C.F. The populations of the developed countries. *Sc Am* 231, 109 - 120.
- Williams, M., Hole, D.J., Murdoch, R.W.G., Ogden, A.C. & Hargreave, T.B. 1980. 48-hour cephadrine and post-prostatectomy bacteriuria. *Br J Urol*, 52, 311 - 315.
- Williams, M. & Hole, D.J. 1982. Bacteriuria in patients undergoing prostatectomy *J Clin Pathol*, 35, 1185 - 1189.
- Winberg, J., Bergström, T., Lincoln, K. & Lidin-Janson, G. 1973. Treatment trials in urinary tract infection with special reference to the effect of antimicrobials on the fecal and periurethral flora. *Clin Nephrol*, 1, 142 - 148.
- Young, H.H. & Davis, D.M. 1926. Young's practice of urology, 1, 496. W.B. Saunders Co., Philadelphia, U.S.A.

I

THE EFFECT OF A SHORT ANTIBIOTIC COURSE IN
TRANSURETHRAL PROSTATIC RESECTION.

M. Grabe, A. Forsgren & S. Hellsten

THE EFFECT OF A SHORT ANTIBIOTIC COURSE IN TRANSURETHRAL PROSTATIC RESECTION

M. Grabe,¹ A. Forsgren² and S. Hellsten¹

From the Departments of ¹Urology and ²Clinical Bacteriology, University of Lund, Malmö General Hospital, Malmö, Sweden

(Submitted for publication March 11, 1983)

Abstract. In a prospective randomized study of 192 patients, the effect of a short course of cefotaxime in connection with transurethral prostatic resection was analyzed. The antibiotic was given to 98 patients, while 94 were assigned to a control group without antibiotic. The frequency of bacteriuria in the cefotaxime group was 43% preoperatively and 18% six weeks postoperatively. In the control group the corresponding figures were 40 and 42% ($p < 0.01$). Complicated postoperative infection did not occur in the cefotaxime group, but in the control group there was one case of septicemia and seven patients had upper urinary tract infections ($p < 0.01$). In the cefotaxime group, patients with preoperatively negative urine culture were prevented from acquiring bacteriuria, and 67% of preoperatively present infections were eliminated at six weeks after the operation, as compared with 30% in the control group. There were essentially no side effects of cefotaxime. Renal function was not influenced by the combination of cefotaxime and furosemide.

Surgery for prostatic obstruction nowadays consists mainly of transurethral resection (TUR) of the prostate, which has greatly reduced the previous morbidity and mortality (Blandy, 1978). Urinary tract infection, however, is a common complication of TUR, and in many patients bacteriuria has been found several weeks or months after the operation (Creevy & Feeney, 1954). Whereas most authors agree that patients with bacteriuria preoperatively should be treated before TUR, the benefit of prophylactic use of antibiotic in non-bacteriuric patients is a more controversial question, and the same applies to the choice of drugs and the length of antibiotic treatment (Plorde, Kennedy, Bourne, Ansell & Petersdorf, 1965; Morris, Golowsky, Guinness & Maher, 1976; Williams, Hole, Murdoch, Ogden & Hargreave, 1980; Shah, Williams & Chaudary, 1981).

The aim of the study here presented was to evaluate the effect of a short course of a potent antibiotic (cefotaxime) in patients undergoing pros-

tatic surgery. The frequency of postoperative bacteriuria, the infectious complications and the side effects of cefotaxime were registered during the six-week period following the operation.

MATERIAL AND METHODS

Patients. The study comprised 192 patients who were to undergo TUR for prostatic obstruction. Excluded from the study were patients with hypersensitivity to penicillin or cephalosporins, patients who had received antibiotics during the week prior to TUR and those with serum creatinine higher than 115 $\mu\text{mol/l}$. Of the 192 patients, 98 were randomly assigned to the antibiotic (cefotaxime) group and 94 to a control group without antibiotic. The mean age at TUR was 71 years (Table I). Carcinoma of the prostate was the cause of obstruction in 46 cases (24%). The mean stay in hospital was 7.1 days in the antibiotic group and 7.9 days in the controls. An indwelling catheter was required before TUR by 37% of the patients.

Urine cultures. The outline of the study is presented in Fig. 1. Samples of urine were taken for culture preoperatively (A, 2 cultures), when the indwelling catheter was removed after TUR (B) and approximately 10 days (C) and 6 weeks (D) after TUR. Cultures were made from voided midstream urine collected after washing of the external genitals, and the bladder incubation time was 4 hours when possible.

The samples were immediately refrigerated and bacteriologic processing usually was begun within 1 to 2 hours. Cultures were run with routine quantitative assay on blood agar plates and on a variant of LSU (medium 32) agar (Juhlin & Ericsson, 1961). Isolated bacteria were identified with conventional biochemical tests (Cowan & Steel, 1970) and their sensitivity to antibiotics was assessed with a disc diffusion method (Ericsson & Sherris, 1971) on PDM Antibiotic Sensitivity Medium agar (Biodisk, Stockholm).

In 179 of the 192 patients (92 in the cefotaxime group and 87 in the control group) preoperative urinary cultures and postoperative follow-up could be made for evaluation of bacteriuria. At 10 days after TUR 170 patients (88 and 82 in respective groups) and at 6 weeks 156 (80 and 76 respectively) could be studied for bacteriuria (Fig. 2).

Table I. Clinical data on 192 patients undergoing TUR

	Cefotaxime	Controls	Total
No of patients	98	94	192
Age, yrs (mean & range)	71.7 (56-86)	70.9 (39-88)	71.3
Hospitalization, days (mean)	7.1	7.9	7.5
Days from operation to discharge (mean)	4.4	5.1	4.7
% with indwelling catheter before operation	42	31	37
% with prostatic cancer	20	28	24
Weight of resected prostate, g (mean & range)	16.1 (2-70)	15.6 (2-113)	15.8

Blood samples. On the day of admission blood was sampled for red and white cell count, platelet count and determination of hemoglobin, sodium, potassium, creatinine, urea, bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase. These analyses were repeated during and after treatment with cefotaxime and one week after discharge from hospital.

Surgical procedure. TUR was performed by five surgeons, using a standardized technique. Perioperatively the bladder was irrigated with sterile glycine (2.2%). Closed bladder drainage was maintained postoperatively. Forced diuresis was induced during the operation by intravenous injection of 40 mg furosemide. High diuresis was maintained during the following 24 hours by intravenous infusion of 3-6 liters of crystalloid solution (Ringer-glucose 2.5%, fructose 15%—glucose 5.5%) to which was added 20 mg furosemide/l. The total of intravenously administered furosemide generally was 80-120 mg. The indwelling catheter was removed 1-3 days after TUR, except in a few patients who required longer catheterization.

Treatment schedule. The first 71 patients in the cefotaxime group received the drug in a dosage of 0.75 g twice daily by intramuscular injection, and the following 27 patients were given 1 g once daily. The first dose of cefotaxime was given on the evening before TUR, the second at the time of the preoperative medication and the final dose on the day when the indwelling catheter was removed. Most of the patients were discharged from hospital 1-2 days later. The patients in the control group received no antibiotics up to 6 weeks after the TUR, unless infectious complications arose. After 6 weeks even patients with asymptomatic but significant bacteriuria received antibiotics in accordance with the sensitivity pattern of the isolated organisms.

Definitions. A bacterial count of $>10^5$ /l urine was defined as significant bacteriuria, and counts of 10^7 - 10^8 /l urine were classified as non-significant bacteriuria.

Postoperative septicemia was defined as positive blood culture with high fever and systemic symptoms. Postoperative upper urinary tract infection was diagnosed on a clinical basis as positive urine culture and fever associated with flank pain and/or systemic symptoms. Postoperative lower urinary tract infection, also by clinical definition, was positive urine culture associated with symptoms of cystitis.

Comparability. The antibiotic group and the control

group were comparable in terms of age and concomitant disease, operation procedure, frequency of malignancy in the resected prostate specimen, weight of resected prostate, postoperative care and time of hospitalization (Table I). The follow-up schedule was the same in both groups.

Statistical methods. Tests for statistical significance were made with the two-by-two chi-square test or with Fisher's exact test. Means were compared according to normal and *t*-distribution as required.

RESULTS

Bacteriuria

The frequency of bacteriuria in *all patients* preoperatively and at early and late follow-up after TUR is presented in Fig. 2 (divided in bacterial counts 10^7 - 10^8 organisms per liter and $>10^8$ organisms per liter urine). On admission (A) the cefotaxime group and the control group were almost equal regarding bacteriuria (43 and 40%, respectively). At the time of catheter withdrawal (B) there was only one case of (non-significant) bacteriuria in the cefotaxime group, but 60% in the control group. At 10 days (C) and 6 weeks (D) after TUR, the figures in the

STUDY OUTLINE

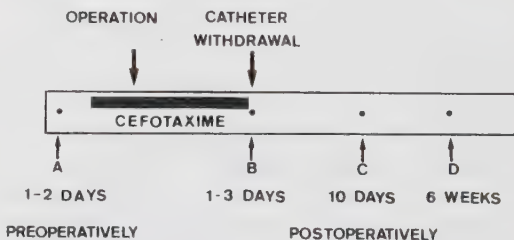


Fig. 1. Time schedule of the study, indicating urine cultures (A-D) in relation to the clinical procedure and the time of antibiotic treatment.

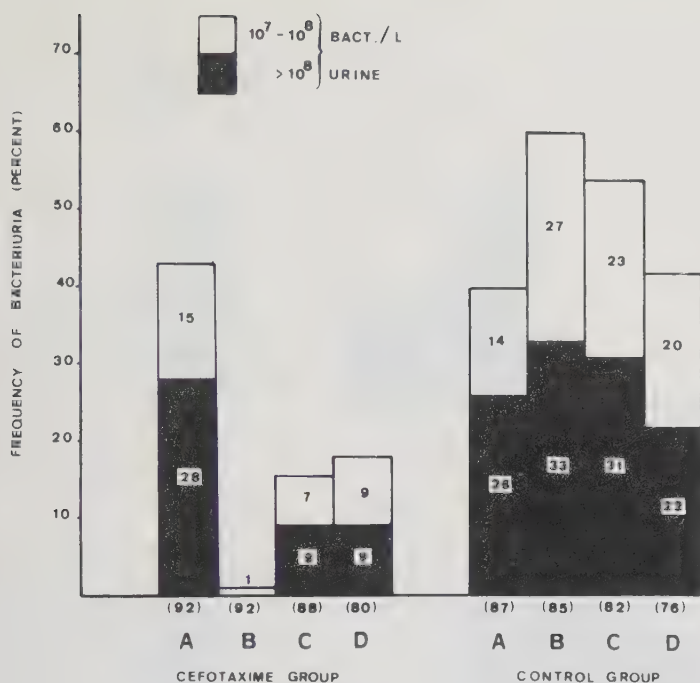


Fig. 2. Frequency of bacteriuria in all patients of the cefotaxime and the control group. A-D = culture times as shown in Fig. 1. Figures in brackets indicate the total of investigated patients.

cefotaxime group were 16 and 18%, while in the controls they were 54 and 42%. The intergroup difference was significant at 10 days ($p < 0.001$) and at 6 weeks ($p < 0.01$).

The frequency of bacteriuria in the patients *without bacteriuria before TUR* is demonstrated in Fig. 3. In the cefotaxime group no patient had significant bacteriuria postoperatively, but a few patients had non-significant bacteriuria at the time of catheter withdrawal and at 10-day and 6-week follow-up (2, 5 and 7%, respectively). In the control group altogether 42% had bacteriuria at catheter withdrawal and 40 and 29% on the follow-up occasions. The intergroup difference was highly significant ($p < 0.001$).

The findings in the patients with *significant pre-operative bacteriuria* are surveyed in Fig. 4. Of the 26 patients in the cefotaxime group, all were bacteria-free after TUR, but after 10 days there was recurrence in 8 of 23 examined patients and after 6 weeks in 7 of 21. Thus bacteriuria was eliminated in 65% of cases after 10 days and in 67% after 6 weeks. Among the 23 patients of the control group there was elimination of bacteriuria in only 14% after 10 days and 30% after 6 weeks. The intergroup difference was statistically significant on

both occasions ($p < 0.001$ at 10 days, $p < 0.02$ at 6 weeks).

Urinary tract infection

Table II shows that none of the cefotaxime group but seven controls had infection of the upper urinary tract in the postoperative period ($p < 0.01$). These infections appeared within the first week after TUR, and prolonged the mean hospital stay

Table II. Infectious complications in the first 6 weeks after TUR in 192 patients

Complications	No. of complications	
	Cefotaxime group (n=98)	Control group (n=94)
Septicemia	0	1 (patient died)
Upper urinary tract infection	0	7
Symptomatic lower urinary tract infection	4	9
Epididymitis	1	1
Total	5	18 ^a

^a Complications significantly fewer in the cefotaxime than in the control group ($p < 0.01$).

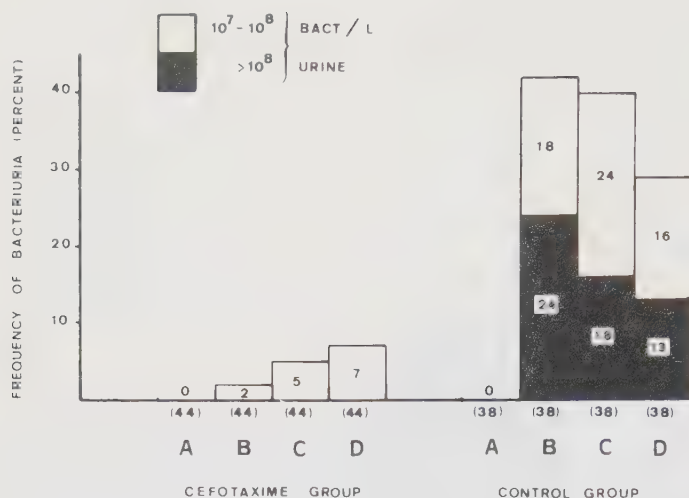


Fig. 3. Occurrence of bacteriuria in the 44 patients from the cefotaxime group and 38 from the control group without preoperative bacteriuria (all cultures available). Sampling times as in Fig. 1.

from 7.5 to 10.6 days. No correlation was found between upper urinary tract infection and preoperative bacteriuria (3 of the 7 patients had had positive cultures) or with cancer of the prostate (3/7) or preoperative indwelling catheter (2/7), which thus were not identifiable as risk factors. Table II further shows that symptomatic lower urinary tract infection complicated the postoperative period in 4 of the patients receiving cefotaxime and in 9 of the controls while in each group there was 1 case of epididymitis.

Fatal complications

Two patients died. Both were in the control group. One death was due to perioperative cardiac arrest and the other to postoperative septicemia, severe bleeding and cardiac failure. The latter patient was the only one with a positive blood culture supporting the diagnosis of septicemia (*E. coli* with serotype and antibiotic sensitivity pattern the same in blood culture and in preoperative urine culture).

Temperature

In a limited sequential group involving 22 patients in the cefotaxime group and 20 controls, the charted morning and evening temperatures were analyzed. There was no significant intergroup difference.

Renal function

Slight increase of serum urea and creatinine was found in most patients 1-3 days after TUR, but the

preoperative level was regained within a week. There was no difference in these respects between the patients receiving cefotaxime and furosemide and those receiving only furosemide. Consequently, renal function appeared to be uninfluenced by cefotaxime, even when combined with furosemide.

DISCUSSION

Since TUR became the method of choice for removal of prostatic obstruction, the postoperative morbidity and mortality have decreased and reduction of hospital stay has been achieved. Modern care in association with TUR involves careful aseptic management during and after the operation, use of a closed system for bladder drainage, a short period of catheterization and either aseptic external irrigation or use of forced diuresis induced by a 'loop' diuretic. Postoperative infectious complications still occur, however. Antibiotics given in conjunction with TUR have been shown to reduce the rate of such complications (Plorde et al.; Shah et al.; Williams et al.; Hargreave, Hindmarsh, Elton, Chisholm & Gould, 1982), though the available literature does not permit definite conclusions concerning the benefit of a course of antibiotics, drugs of choice or treatment schedules (Chodak & Plaut, 1979).

The present randomized trial comprised patients undergoing TUR for prostatic obstruction whether or not bacteriuria was present and/or indwelling catheter inserted before the operation. Cefotaxime

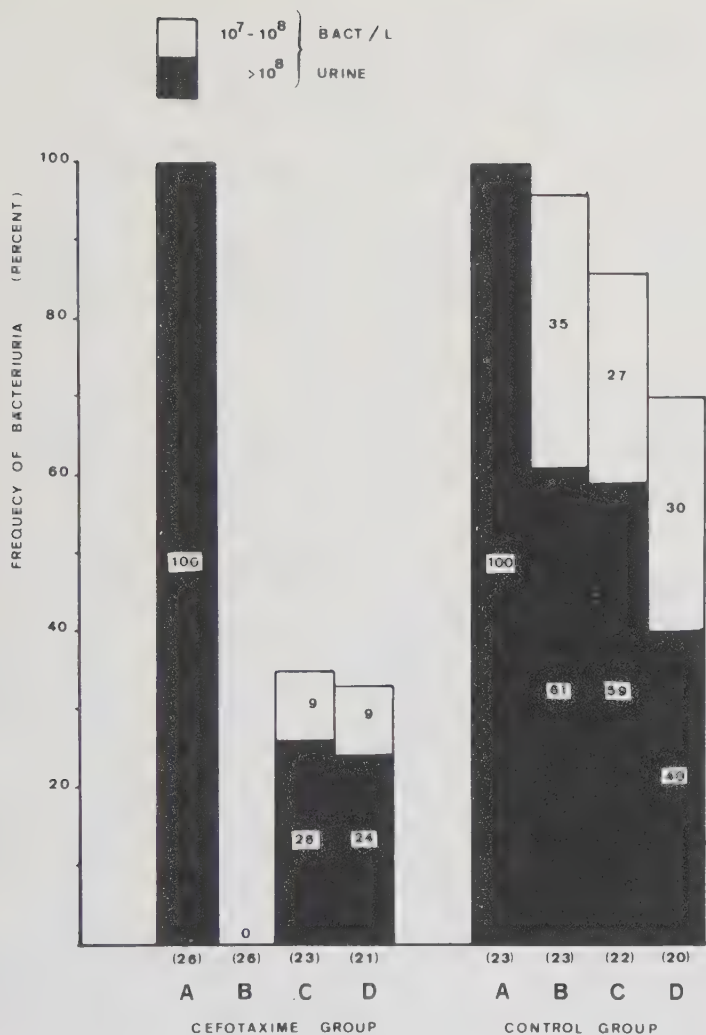


Fig. 4. Frequency of bacteriuria in 26 patients from the cefotaxime group and 23 from the control group with preoperatively significant bacteriuria. Figures in brackets indicate the numbers of investigated patients. Sampling times as in Fig. 1.

was chosen because of its high activity against pathogens commonly found in the urinary tract (Hamilton-Miller, Brumfitt & Reynolds, 1978), and favorable concentrations demonstrated in serum, urine and prostatic tissue (Grabe, Andersson, Forsgren & Hellsten, 1981). A short parenteral course of the drug before, during and after the operation gave a high serum concentration with minimized risk of development of resistance and of influence on the fecal bacterial flora.

The single case of septicemia (in the control group) permitted no conclusion in regard to the benefit of antibiotics in this respect. A significantly

higher rate of upper urinary tract infection was found among the controls, however, and in these patients hospitalization was prolonged. No preoperative risk factor was found that could explain the infections. Symptomatic infections of the lower urinary tract and epididymitis did not appear to be influenced by the antibiotic prophylaxis.

The number of patients without bacteriuria before TUR was similar in both groups. In the control group, the surgical procedure and the post-operative catheter drainage, though the latter was as brief as possible (usually less than 48 hours), were associated with significant bacteriuria at the time of the

catheter removal in 24% of the patients. Significant bacteriuria persisted in 16% of the patients after 10 days and in 13% after 6 weeks. As no patient in the cefotaxime group had significant bacteriuria after TUR, the results indicated that a short course of a potent antibiotic reduces the risk of postoperative acquisition of bacteriuria.

Among the patients with significant bacteriuria prior to TUR, two-thirds of those in the cefotaxime group were free from significant bacteriuria at follow-up after 6 weeks, as compared with one-third in the control group.

No difference in postoperative body temperature was found between the cefotaxime group and the controls. Other authors (Plorde et al.; Gonzales, Wright & Blackard, 1976) similarly demonstrated slight and transient elevation of body temperature in the immediate postoperative period independently of antibiotics use, which has been regarded as a normal reaction to surgery.

Cefotaxime was well tolerated in all cases and no side effects were observed. With respect to renal function, the study confirmed that cefotaxime can safely be used in combination with furosemide (Mondorf, Burk, Stefanescu, Scherberish & Schoeppe, 1980).

CONCLUSIONS

In patients subjected to TUR of the prostate, whether or not they were bacteriuric preoperatively, a short course of cefotaxime resulted in reduced frequency of postoperative bacteriuria as compared with patients in a control group without antibiotic. The rate of upper urinary tract infections was significantly higher in the control group. Further studies are required to evaluate if such an antibiotic course will reduce long-term morbidity.

REFERENCES

Blandy, J. P. 1978. *Transurethral resection*, 2th ed. Pitman Medical Publishing Co Ltd, Kent, England.

Chodak, G. W. & Plaut, M. E. 1979. Systemic antibiotics for prophylaxis in urologic surgery: A critical review. *J Urol* 121, 695.

Cowan, S. T. & Steel, K. J. 1970. *Manual for the identification of medical bacteria*. Cambridge University Press, London.

Creevy, C. D. & Feeney, M. J. 1954. Routine use of antibiotics in transurethral prostatic resection: A clinical investigation. *J Urol* 71, 615.

Eriessson, H. M. & Sherris, J. C. 1971. Antibiotic sensitivity testing. Report of an international collaborative study. *Acta Pathol Microbiol Scand* (B), Suppl. 217.

Gonzales, R., Wright, R. & Blackard, C. E. 1976. Prophylactic antibiotics in transurethral prostatectomy. *J Urol* 116, 203.

Grabe, M., Andersson, K. E., Forsgren, A. & Hellsten, S. 1981. Concentration of cefotaxime in serum, urine and tissues of urological patients. *Infection* 9, 154.

Hamilton-Miller, J. M. T., Brumfitt, W. & Reynolds, A. V. 1978. Cefotaxime (HR 756) a new cephalosporin with exceptional broad-spectrum activity in vitro. *J Antimicrob Chemother* 4, 437.

Hargreave, T. B., Hindmarsh, J. R., Elton, R., Chisholm, G. D. & Gould, J. C. 1982. Short-term prophylaxis with cefotaxime for prostatic surgery. *Br M J* 284, 1008.

Juhlin, I. & Ericson, C. 1961. A new medium for the bacteriologic examination of stools (LSU-Agar). *Acta Pathol Microbiol Scand* 52, 185.

Mondorf, A. W., Burk, P., Stefanescu, T., Scherberich, J. E. & Schoeppe, W. 1980. Effects of cefotaxime on the proximal tubules of the human kidney. *J Antimicrob Chemother* 6, Suppl. A., 155.

Morris, M. J., Golowsky, D., Guinness, M. D. G. & Maher, P. O. 1976. The value of prophylactic antibiotics in transurethral prostatic resection: A controlled trial, with observations on the origin of postoperative infection. *Br J Urol* 48, 479.

Plorde, J. J., Kennedy, R. P., Bourne, H. H., Ansell, J. S. & Petersdorf, R. G. 1965. Course and prognosis of prostatectomy: With a note on the incidence of bacteremia and effectiveness of chemoprophylaxis. *N Engl J Med* 272, 269.

Shah, P. J. R., Williams, G. & Chaudary, M. 1981. Short-term antibiotic prophylaxis and prostatectomy. *Br J Urol* 53, 339.

Williams, M., Hole, D. J., Murdoch, R. W. G., Ogden, A. C. & Hargreave, T. B. 1980. 48-hour cephadrine and post-prostatectomy bacteriuria. *Br J Urol* 52, 311.

II

SPECIES DISTRIBUTION AND ANTIBIOTIC SENSITIVITY OF
BACTERIA ISOLATED PRE- AND POSTOPERATIVELY FROM
PATIENTS UNDERGOING TRANSURETHRAL PROSTATIC RESECTION

M. Grabe, A. Forsgren & S. Hellsten

ABSTRACT

The identity and antibiotic sensitivity of the isolated bacteria from 179 patients undergoing transurethral resection of the prostate were analysed. The patients were randomized into a group receiving a short course of cefotaxime in conjunction with the operation and a control group given no antibiotics. Preoperatively 70 patients had bacteriuria ($\geq 10^7$ cfu/l) with a predominance of Gram-negative bacteria (57 isolates, mainly *E. coli*, *Enterobacter*, *Klebsiella*, *Proteus*) although Gram-positive species (24 isolates, mainly enterococci and *Staphylococcus epidermidis*) were also frequently encountered. Preoperatively isolated pathogens were evenly distributed in both groups and the sensitivity pattern was comparable. In the cefotaxime group postoperative recurrence of the preoperatively identified bacteria occurred in a lower frequency (11/43) than persistence in the control group (24/38). Only Gram-negative pathogens were isolated from patients with postoperative septicemia and upper urinary tract infections indicating that it is most important to direct prophylaxis against Gram-negative bacteria. A high degree of sensitivity to cefotaxime, gentamicin, trimethoprim, co-trimazine and a combination of ampicillin and mecillinam was recorded among both pre- and postoperatively isolated bacteria.

INTRODUCTION

Urinary tract infection (UTI) is a common complication to transurethral resection (TUR) of the prostate. Infected urine may lead to serious and sometimes fatal complications. However, a reduction in the incidence of infection has been demonstrated by the use of antibiotics in conjunction with TUR (Plorde, Kennedy, Borne, Ansell & Petersdorf, 1965; Hills, Bultitude & Eykun, 1976; Williams, Hole, Murdoch, Ogden & Hargreave, 1980; Hargreave, Hindmarsh, Elton, Chisholm & Gould, 1982).

In a previous publication it was demonstrated that the frequency of bacteriuria after TUR of the prostate was reduced in both preoperatively bacteriuric and non-bacteriuric patients given a short course of cefotaxime compared with patients in a control group that was not given antibiotics (Grabe, Forsgren & Hellsten, 1984). The frequency of upper urinary tract infections was significantly higher in the control group. A rational choice of a suitable antimicrobial agent can only be made when the distribution of the genera of organisms likely to be present and their probable sensitivity are known. As to date the number of investigations on bacteria isolated from patients undergoing TUR is limited (Williams & Hole, 1982), we analysed the identity and antibiotic sensitivity of the bacteria isolated pre- and postoperatively from the patients in our clinical study.

MATERIAL AND METHODS

Patients: One hundred and ninety-two patients who were to undergo transurethral resection of the prostate were included in a prospective, controlled trial as described before (Grabe et al). Ninety-eight patients were randomly assigned to the cefotaxime group and ninety-four to a control group. Patients belonging to the antibiotic group received cefotaxime from the evening before the operation until the day of catheter withdrawal. The mean age of the patients was seventy-one years (range 39 to 88). In the cefotaxime group 42 per cent of the patients and in the control group 31 per cent required indwelling catheter before the operation. In the remaining patients the indwelling catheter was inserted at the operation at first. The catheter was removed usually one to three days postoperatively. In one hundred and seventy-nine patients (92 in the cefotaxime group and 87 in the control group) urinary culture could be followed pre- and postoperatively.

Urine samples and culture: Samples for urine culture were taken preoperatively (2 cultures), the day of the removal of the indwelling catheter (1 culture), approximately 10 days (2 cultures) and 6 weeks (1 culture) after surgery as described before (Grabe et al). Cultures were made from clean voided mid-stream urine and the incubation time was 4 hours when possible. Urine samples obtained from indwelling catheter were collected by aspiration from the tube after cleaning with a wet swab and approximately 30 minutes of clamped tube. Urine culture was performed by a routine quantitative assay on blood agar plates and a variant of LSU agar (medium 32) (Juhlin & Ericsson, 1961). Isolated bacteria ($\geq 10^7$ colony-forming units (cfu) per litre urine) were identified by conventional biochemical tests (Cowan & Steel, 1970) and stored as nutrient agar stab cultures.

Susceptibility tests: The sensitivity of isolated bacteria to antibiotics was assessed immediately after isolation using a disc diffusion method (Ericsson & Sherris, 1971) on PDM agar (AB Biodisk, Stockholm). After the clinical study was completed the minimal inhibitory concentration (MIC-value) of the isolated bacteria were determined with an agar dilution method (Forsgren, 1981). The medium used was PDM-agar and the inoculum consisted of a four-hour-culture diluted in saline to a concentration of 10^{10} bacteria per litre and applied to the surface of the agar in 1-2 μ l quantities with the aid of multipoint inoculator. Ampicillin (AS 360 Leo, Denmark), mecillinam (81 12 10 Leo, Denmark), cefalexin (81 A 729, Lilly), cefotaxime (Hoechst 65), gentamicin (81 B 2602, Schering corp.), nalidixic acid (214/554, Sterling Winthrop), nitrofurantoin (87367, Pharmacia, Sweden), trimethoprim (27657-52/Kabi, Sweden), co-trimazine (trimethoprim/sulphadiazine:18 %/82 %) (82 01 11, Astra, Sweden) were tested.

The evaluation of resistance and sensitivity respectively was based on the SIR-system (The Swedish reference group for antibiotics, 1981). For co-trimazine a break-point of 8 μ l/ml was used.

Serotyping: O:H and K-serotyping of E. coli strains were kindly performed by Dr. I. Ørskov, WHO International Escherichia Centre, Statens Seruminstitut, Copenhagen, Denmark.

RESULTS

The bacterial species isolated pre- and postoperatively from patients undergoing TUR are presented in Table I. Gram-negative species predominated.

Table I. Bacterial isolates ($> 10^7$ cfu/l) from 179 patients 1-2 days before transurethral prostatic resection, recurring and persisting respectively after surgery and acquired by preoperatively non-bacteriuric patients at any time until 6 weeks postoperatively.

Species	NUMBER OF ISOLATES					
	Cefotaxime group (n = 92)			Control group (n = 87)		
	Preop.	Recurr.	Acquired	Preop.	Persist.	Acquired
<i>E. Coli</i>	9	2	-	6	5	6
<i>Proteus mirabilis</i>	4	1	-	7	5	2
<i>Klebsiella</i>	9	0	-	4	4	1
<i>Enterobacter</i>	4	2	-	5	5	2
<i>Proteus morgani</i> , <i>vulgaris</i> , <i>rettgeri</i>	3	1	1	-	-	-
<i>Citrobacter</i>	-	-	-	1	0	-
<i>Acinetobacter</i>	-	-	-	1	0	-
<i>Pseudomonas aeruginosa</i> , <i>malophilia</i>	1	0	-	3	0	-
<i>Enterococci</i>	5	3	2	6	2	4
<i>Staph. epidermidis</i>	5	1	1	3	2	7
<i>Staph. aureus</i>	3	1	-	2	1	-
Total bacteria	43	11	4	38	24	22
Total patients	38	11	4	32	24	21

Escherichia coli and *Klebsiella* species were the most often encountered isolates. Gram-positive bacteria like enterococci and staphylococci were also frequently recorded. Preoperatively the cefotaxime group and control group were comparable in terms of species and number of isolates. However, postoperatively the number of isolates was significantly lower in the cefotaxime group than in the control group.

All patients in the cefotaxime group still being covered by the antibiotic had negative urine culture on the day of the catheter removal. However, in 11 patients the same bacteria as found preoperatively *recurred* postoperatively as is shown by the same sensitivity pattern and for *E. coli* identical serogroups. No change in the inhibition zones was recorded for cefotaxime by the disc diffusion method postoperatively compared with preoperatively. In the cefotaxime group there was a higher frequency of recurrent Gram-positive than Gram-negative isolates, i.e. five out of thirteen Gram-positive compared to six out of thirty Gram-negative (Table I). Ten out of the eleven patients with recurrence of the preoperative isolated bacteria had indwelling catheter before the operation. The remaining patient had a chronic prostatitis as shown by the microscopic examination of the resected prostate.

In the control group there was a *persistence* of the same bacterium in twenty-four patients as shown by identical antibiotic sensitivity pattern and serotype (*E. coli*). Nineteen out of the twenty-four patients had indwelling catheter before the operation. All but one of the remaining five patients had reasonable focus for persistence of bacteriuria such as chronic pyelonephritis, urethral stricture or obstruction of upper urinary tract due to prostatic cancer.

The frequency of *acquired bacteriuria* (defined as $\geq 10^7$ cfu/l urine acquired at any time postoperatively in preoperatively non-bacteriuric patients) after transurethral prostatic resection was 55 per cent (21 patients acquired bacteriuria out of 38 preoperatively non-bacteriuric patients) in the control group and 9 per cent (four out of forty-four) in the cefotaxime group. No difference in species distribution of preoperative isolates compared with the postoperatively acquired pathogens was observed except for an increased presence of enterococci and *Staphylococcus epidermidis*.

Only Gram-negative bacteria were isolated from the eight patients with septicemia and with upper urinary tract infection as shown in Table II. Four of the patients had bacteriuria preoperatively and from three of them the same

Table II. Isolated bacteria from 8 patients with postoperative severe infectious complications (< 1 week).

Patient nr.	I s o l a t e s	
	Preoperatively (urine)	Postoperatively (blood or urine)
1*	E. coli	E. coli (blood)
2**	Enterobacter	Enterobacter, E. coli (Urine)
3.	E. coli	negative urine (antibiotic treatment)
4	Klebsiella	Klebsiella (urine)
5	negative	E. coli (urine)
6	negative	E. coli, Proteus mirabilis (urine)
7	negative	Klebsiella (urine)
8	negative	Enterobacter (urine)

* Septicemia

** nr 2-8: upper urinary tract infection

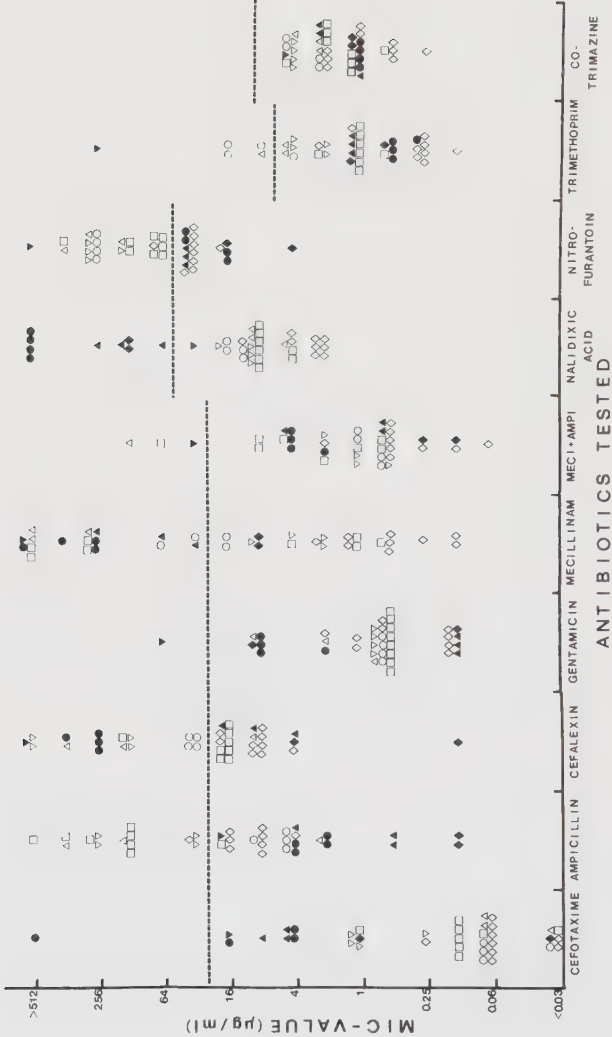


Fig 1. Preoperative bacterial isolates in the cefotaxime group. Symbols above the dotted line indicate resistance to the drug according to the SIR system. Two Staphylococcus aureus strains were beta-lactamase producing. Five isolates were not available for analysis. Symbols: E. coli (◇); Klebsiella (□); Pseudomonas aeruginosa (▽); Proteus mirabilis (○); other Proteus (△); Enterobacter (▽); Acinetobacter (■); enterococci (●); Staphylococcus aureus (▲); Staphylococcus epidermidis (◆).

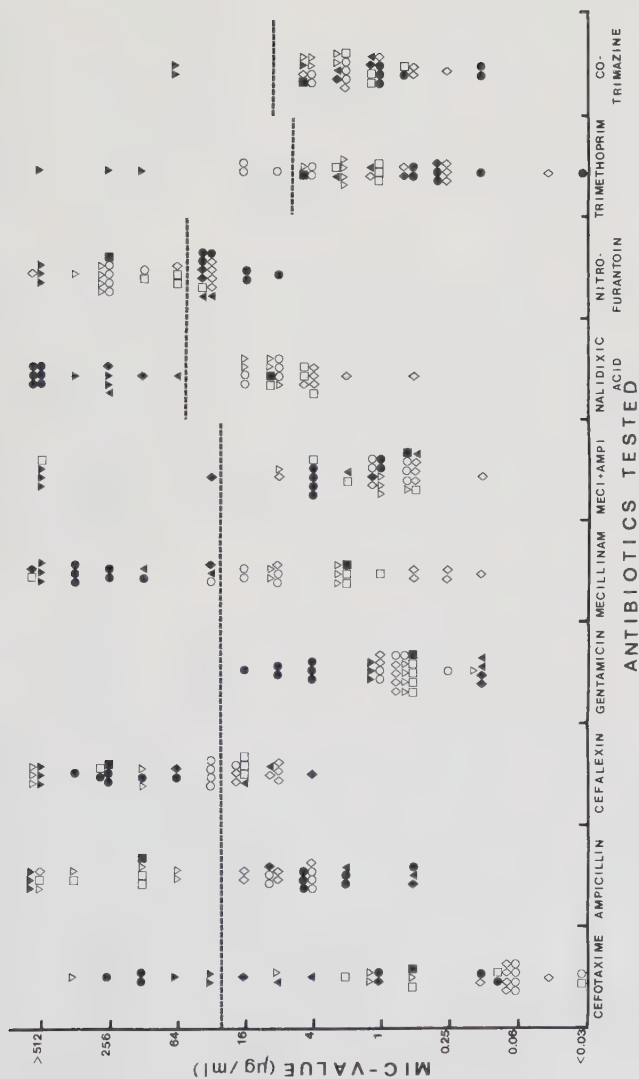


Fig 2. Preoperative bacterial isolates in the control group. Symbols above the dotted line indicate resistance to the drug. Two *Staphylococcus epidermidis* and one *Staphylococcus aureus* were beta-lactamase producing. Four isolates were not available for analysis. Symbols as described in Fig 1.

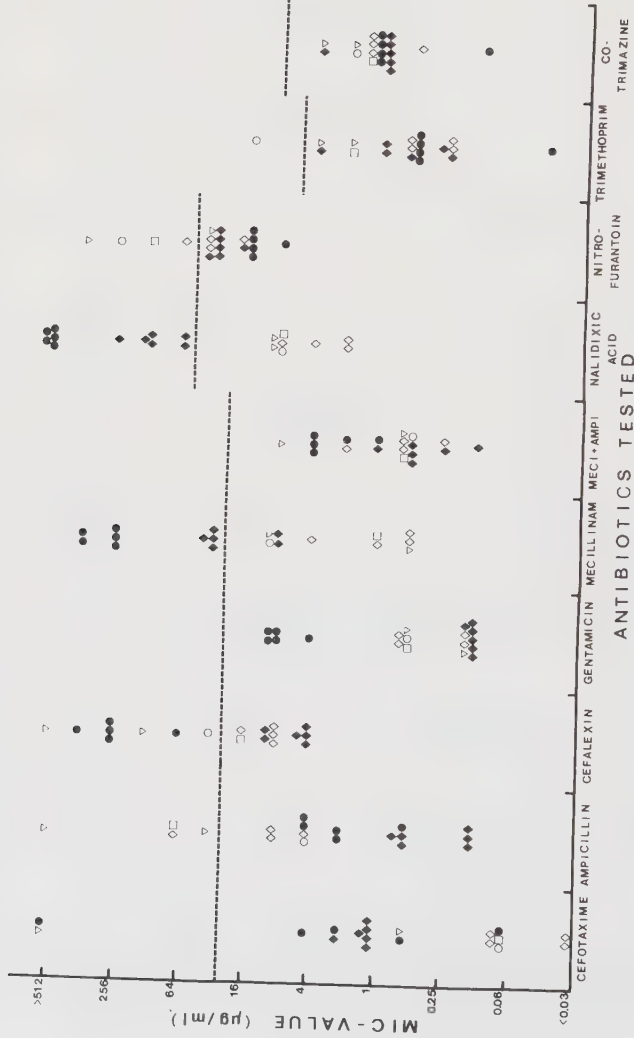


Fig 3. Postoperative acquired bacterial isolates in both groups. Symbols above the dotted line indicate resistance to the drug. Three *Staphylococcus epidermidis* strains were beta-lactamas producing. Three isolates were not available for analysis. Symbols as described in Fig 1.

organism could be isolated postoperatively (same sensitivity pattern). In one patient antibiotic treatment was initiated before postoperative culture was taken.

In four patients postoperatively acquired bacteriuria was associated with upper urinary tract infection (patient 5 to 8 in Table II).

The antibiotic sensitivity pattern for bacteria *isolated preoperatively* from patients in the cefotaxime and control group respectively is presented in figure 1 and 2. The data do not reveal any major difference between the isolates from the two groups. Low MIC-values, i.e. remarkable effect *in vitro* against most isolates were seen for cefotaxime, the drug used in the clinical study. However, a few isolates of enterococci, *Pseudomonas aeruginosa* and *Enterobacter* were resistant.

Figure 3 demonstrates the species and antibiotic sensitivity pattern for bacteria *acquired postoperatively* in both the cefotaxime- and control group. The same antibiotic pattern as for bacteria isolated preoperatively was observed. All but two of the acquired pathogens had MIC-values below eight $\mu\text{g/ml}$ for cefotaxime. The figures also demonstrate that a high degree of efficacy was reached by gentamicin, trimethoprim, co-trimazine and the combination of ampicillin and mecillinam. Other antibiotics like ampicillin and cefalexin had a lower effect.

DISCUSSION

Inconsistency in study design and limited interest given to the pathogens present before and after operation and hospital exposure characterize the available literature regarding the use of antimicrobial agents in prostatic surgery (Berger & Nagar, 1978; Chodak & Plaut, 1979). Therefore we conducted a bacteriological analysis of the pre- and postoperatively isolated bacteria in addition to the clinical assessment earlier presented (Grabe et al). In all but one patient in whom bacteriuria *recurred or persisted* postoperatively a reason could be found. The patients had either had an indwelling catheter inserted preoperatively for several weeks or months, or an infectious focus could be observed such as chronic prostatitis, chronic pyelonephritis or upper urinary tract obstruction due to prostatic cancer. The relapse of bacteriuria in patients with indwelling catheter before operation is obvious in this study. We therefore concluded that such patients are all at risk for postoperative

bacteriuria and immediate postoperative severe infectious complications and are eligible for receiving antibiotics when they are to undergo TUR.

Previous reports on the incidence of postoperatively acquired infections vary from 6.4 to 69.7 per cent (Genster & Madsen, 1970; Brehmer & Madsen, 1972; Symes, Hardy, Sutheris & Blandy, 1972; Shapiro, Santamarina & Harrison, 1974; Collste & Törnqvist, 1978; Williams et al). In our material 55 per cent of the preoperatively non-bacteriuric patients in the control group acquired bacteriuria and in four of them upper urinary tract infection arose. As no such events were observed in the antibiotic group we conclude that the high level of postoperatively acquired infections also amply justifies the routine prophylactic administration of antimicrobial agents. Several reports have suggested the beneficial effect of antibiotics in transurethral prostatectomy, but to our knowledge only one study (Hargreave et al) beside our own (Grabe et al) has shown a statistical reduction in postoperative complications in addition to the effect on bacteriuria per se. In both studies cefotaxime was used. As shown in Figure 1 - 3 cefotaxime is a cephalosporin with a broad spectrum of remarkable high activity. Our choice of cefotaxime, based on both the antimicrobial properties and the favourable concentrations obtained in urine and tissues of urological patients (Grabe, Andersson, Forsgren & Hellsten, 1981) may explain the significant reduction in bacteriuria and infectious complications.

Many of the pre- and postoperative isolates showed a rather high degree of resistance to commonly used antibiotics like ampicillin, cephalixin, mecillinam, nalidixic acid and nitrofurantoin. Thus it is less likely that these antibiotics should prevent postoperative bacteriuria and associated complications effectively. On the other hand antibiotics like a combination of ampicillin and mecillinam (Miraxid), trimethoprim, co-trimazine and gentamicin demonstrated a similar degree of activity *in vitro* as cefotaxime. However, the choice of antibiotics cannot only be based on its *in vitro* antibacterial activity. Factors like pharmacokinetics, toxicity and the development of resistance also have to be brought into consideration.

A rational choice of a suitable antimicrobial agent can only be made when types of organisms likely to be present and their sensitivity pattern are known. In our study Gram-negative bacteria predominated preoperatively but enterococci and *Staphylococcus epidermidis* were also relatively frequently isolated which recently has been reported by others (Maskell & Pead, 1980; Williams et al). Furthermore there is a substantial number of patients acquiring Gram-positive

organisms postoperatively. Enterococci are known to be fairly resistant to cefotaxime but MIC-determination in the present study was done on PDM-agar which gives favourable results for cefotaxime against enterococci (Forsgren, unpublished results). Due to the relative resistance against enterococci the number of recurrence by this organism was relatively high (three out of five) in the cefotaxime group. However, not a single patient had septicemia or upper urinary tract infection caused by Gram-positive organisms. This fact may be explained by a low capacity of these bacteria to establish such infections. It can be concluded that antibiotic prophylaxis should primarily be focused on Gram-negative bacteria.

Except for an increased rate of *Staphylococcus epidermidis* and enterococci postoperatively there was no difference in species distribution and antibiotic sensitivity pattern among bacteria acquired postoperatively during and after hospitalization compared with preoperative cultures. Essentially similar results have been reported by others (Williams et al). This fact supports the theory that most of the patients acquiring bacteriuria postoperatively were infected in a similar way as the patients becoming bacteriuric preoperatively, i.e. by the pathogens present in the perineum and urethra via the indwelling catheter and that no particular nosocomial strains are involved.

REFERENCES

- Berger, S.A. & Nagar, H. 1978. Antimicrobial prophylaxis in urology. *J Urol*, 120, 319.
- Brehmer, B. & Madsen, P.O. 1972. Route and prophylaxis of ascending bladder infection in male patients with indwelling catheters. *J Urol*, 108, 719.
- Chodak, G.W. & Plaut, M.E. 1979. Systemic antibiotics for prophylaxis in urologic surgery: A critical review. *J Urol*, 121, 695.
- Collste, L.G. & Törnqvist, H. 1978. Urinary infection and transurethral prostatectomy. *Scand J Urol Nephrol*, 12, 7.
- Cowan, S.T. & Steel, K.J. 1970. Manual for the identification of medical bacteria. *Cambridge University Press, London*.
- Ericsson, H.M. & Sherris, J.C. 1971. Antibiotic sensitivity testing. Report of an international collaborative study. *Acta Pathol Microbiol Scand* (B) Suppl, 217.
- Forsgren, A. 1981. Comparative in vitro activity of first and second generation cephalosporin. *Acta Pathol Microbiol Scand* (B), 89, 221.
- Genster, H.G. & Madsen, P.O. 1970. Urinary tract infections following transurethral prostatectomy: With special reference to the use of antimicrobials. *J Urol*, 104, 163.
- Grabe, M., Andersson, K-E, Forsgren, A. & Hellsten, S. 1981. Concentration of cefotaxime in serum, urine and tissues of urological patients. *Infection*, 9, 154.
- Grabe, M., Forsgren, A. & Hellsten, S. 1983. The effect of a short-term antibiotic course in transurethral prostatic resection. *In press*.
- Hargreave, T.B., Hindmarsh, J.R., Elton, R., Chisholm, G.D. & Gould, J.C. 1982. Short-term prophylaxis with cefotaxime for prostatic surgery. *Br Med J*, 284, 1008.
- Hills, N.H., Bultitude, M.I. & Eykyn, S. 1976. Co-trimoxazole in prevention of bacteriuria after prostatectomy. *Br Med J*, 2, 498.
- Juhlin, I. & Ericsson, C. 1961. A new medium for bacteriological examination of stools (LSU-Agar). *Acta Pathol Microbiol Scand*, 52, 185.
- Maskell, R. & Pead, L. 1980. Trimethoprim alone (letter). *The Lancet*, July 19, 144.
- Plorde, J.J., Kennedy, R.P., Bourne, H.H., Ansell, J.S. & Petersdorf, R.G. 1965. Course and prognosis of prostatectomy: With a note on the incidence of bacteremia and effectiveness of chemoprophylaxis. *New-Engl J Med*, 272, 269.
- Shapiro, S.R., Santamarina, A. & Harrison, J.H. 1974. Catheter-associated urinary tract infection: Incidence and a new approach to prevention. *J Urol*, 112, 659.
- Symes, J.M., Hardy, D.G., Sutherns, K. & Blandy, J.P. 1972. Factors reducing the rate of infection after transurethral surgery. *Br J Urol*, 44, 582.

- The Swedish reference group for antibiotics. 1981. A revised system for antibiotic sensitivity testing. *Scand J Infect Dis* 13:148 - 152.
- Williams, M., Hole, D.J., Murdoch, R.W.G., Ogden, A.C. & Hargreave, T.B. 1980. 48-hour cephradine and postprostatectomy bacteriuria. *Br J Urol*, 52, 311.
- Williams, M. & Hole, D.J. 1982. Bacteriuria in patients undergoing prostatectomy. *J of Cl Pathol*, 35, 1185.

III

A SHORT ANTIBIOTIC COURSE GIVEN IN CONJUNCTION WITH
AND AFTER CATHETER REMOVAL CONCECUTIVE TO TRANSURETHRAL
PROSTATIC RESECTION.

M. Grabe, A. Forsgren & S. Hellsten

ABSTRACT

In a prospective randomized study of 96 patients, the effect of a short antibiotic course given after transurethral prostatic resection was analysed. Cefotaxime (1 g. i.m. every 12 hours to a total of 3 g) was given to 47 patients with the first dose when the postoperative catheter was removed while 49 were assigned to a control group without antibiotic. The frequency of bacteriuria was 48 per cent preoperatively in the cefotaxime group and 33 per cent six weeks postoperatively. In the control group the corresponding figures were 63 per cent and 50 per cent ($p > 0.1$). There were two cases of septicemia in each group immediately postoperatively whereas upper urinary tract infection developed in five patients in the control group and one patient in the cefotaxime group ($p > 0.1$). All complications, infectious and non-infectious, were significantly more frequent in the control group (22) compared to the cefotaxime group (12) ($p < 0.05$). The patients receiving the antibiotic remained a shorter time in hospital compared to the controls. Bacteriological analysis showed a good in vitro effect of cefotaxime on isolated bacteria.

INTRODUCTION

Transurethral resection (TUR) is nowadays the main type of operation for prostatic obstruction. Septicemia and upper urinary tract infections are uncommon but severe complications and bacteriuria is observed in a large number of patients postoperatively. The benefit of antibiotics given in conjunction with TUR remains a controversial question (Genster & Madsen, 1970; Berger & Nagar, 1978; Chodak & Plaut, 1979) although more recently, controlled trials emphasize that a short antibiotic course covering the operation and the early postoperative period, usually the period of postoperative catheterization, reduces the frequency of postoperative bacteriuria (Williams, Hole, Murdoch, Ogden & Hargreave, 1980; Ramsay & Sheth, 1983; Grabe, Forsgren & Hellsten, 1984a) and of infectious as well as other complications (Hargreave, Hindmarsh, Elton, Chisholm & Gould, 1982; Grabe et al, 1984a).

In this study we considered an alternative approach by giving a short course of a potent antibiotic (cefotaxime) exclusively postoperatively, starting at the time of catheter removal. The aim was to analyse in a controlled trial if such a scheduled antimicrobial course would a) reduce the frequency of postoperative bacteriuria compared to that prevailing preoperatively, b) protect preoperatively non-bacteriuric patients from acquiring bacteriuria, c) eliminate bacteriuria among patients with preoperatively infected urine and, d) modify the rate of postoperative complications whether infectious or not. In addition we carried out a bacteriological analysis and the isolates were tested against cefotaxime, the trial drug, and ampicillin, a commonly used urinary tract antibiotic. The follow-up for bacteriuria covered a period of four months after the operation. The tolerance and the side effects of the drug were registered.

MATERIAL AND METHODS

Patients: The study comprised 96 patients who were to undergo TUR for prostatic obstruction. Excluded from the trial before randomization were patients with hypersensitivity to penicillin or cephalosporins and patients who had received antibiotics during the week before admission for operation. Of the 96 patients 47 were assigned to receive the antibiotic (cefotaxime group) and 49 to a control group without antibiotic. The mean age of the patients was 71 years in the cefotaxime group and 74 in the control group. In 17 out of 96 patients (18%) the obstruction was caused by a prostatic cancer. Twenty-three patients (49%) in the cefotaxime group and 29 (59%) in the control group required indwelling catheter before admission for surgery (table I).

Surgical procedure: TUR was carried out by 7 surgeons using a standardized technique. Peroperatively the urinary bladder was irrigated with sterile glycine (2.2%). Closed bladder drainage was maintained postoperatively. Forced diuresis was induced during the operation by intravenous injection of 40 mg of furosemide. High diuresis was maintained during the following 24 hours by intravenous infusion of 3 to 6 litres of crystalloid solution (Ringer-glucose 2.5%, fructose 15% - glucose 5.5%) to which was added 20 mg of furosemide per litre. The total of furosemide intravenously administered was generally 80 to 120 mg. The indwelling catheter was removed 1 to 3 days after TUR (mean 1.9 days), except in a few patients who required longer catheterization.

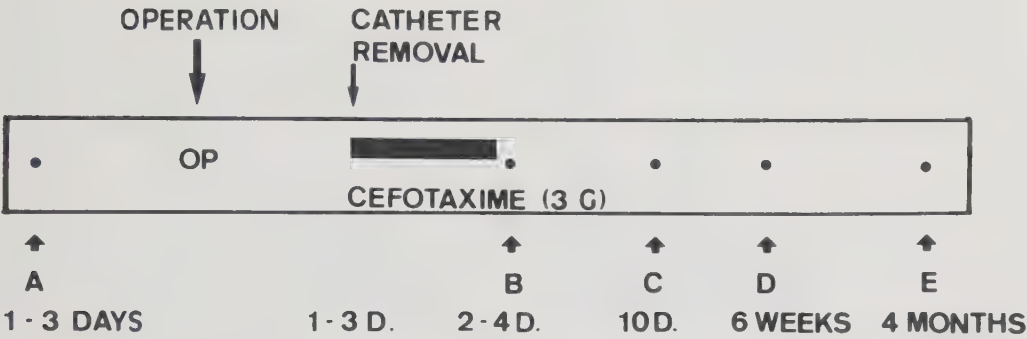
Treatment schedule: 1 g of cefotaxime was given i.m. every 12 hours to a total of 3 g with the first dose given on the day of removal of the indwelling catheter. Most patients were discharged from hospital 1 to 2 days later. The patients in the control group received no antibiotics unless infectious complications arose. Furthermore no antibiotics were given to patients in any of the groups during the first 6 weeks after TUR, unless symptomatic infection was evident.

Definitions: A bacterial count of $> 10^8$ bacteria per litre was defined as significant bacteriuria and counts of 10^7 to 10^8 bacteria per litre urine were classified as non-significant bacteriuria.

Postoperative septicemia was defined as positive blood culture with high fever and systemic symptoms. Postoperative upper urinary tract infection (upper UTI) was diagnosed on a clinical basis as a positive urine culture and fever associated with flank pain and/or systemic symptoms. Postoperative lower urinary tract infection (lower UTI), also by clinical definition, was positive urine culture associated with symptoms of cystitis. Severe postoperative bleeding was considered in those instances when frequent bladder evacuation and/or irrigation was required during the early postoperative period.

Urine culture: The outline of the study is presented in fig. 1. Samples for urine culture were taken preoperatively (A), the day of discharge from hospital (B), approximately 10 days (C), six weeks (D) and four months (E) after TUR. Cultures were made from voided mid-stream urine collected after cleaning of the external genitals. The bladder incubation time was four hours when possible. Urine samples obtained from indwelling catheter were collected by aspiration from the tube after cleaning with a wet swab and clamping of the tube for approximately 30 minutes. The samples were immediately refrigerated

FIG. I. STUDY OUTLINE



PREOPERATIVELY

POSTOPERATIVELY

Fig 1. Time schedule of the study, indicating urine cultures (●; A-E) in relation to the clinical procedure and the time of antibiotic treatment.

Table I. Clinical data on 96 patients undergoing TUR.

	Cefotaxime group	Control group	Total
No of patients	47	49	96
Age, Years (mean & range)	70.7 (53-84)	73.8 (60-88)	72.0
Hospitalization, days (mean)	6.9	8.5	7.7
Days from operation to discharge (mean)	4.4	5.9	5.1
No (%) patients with indwelling catheter before operation	23 (49%)	29 (59%)	52 (54%)
No (%) patients with prostatic cancer	6 (13%)	11 (22%)	17 (18%)
Weight of resected prostate, g (mean & range)	24.1 (2-116)	22.9 (3-65)	23.5
No of days with postoperative indwelling catheter	1.9	1.8	1.85

and bacteriological processing usually initiated within 1 to 2 hours. Cultures were performed by a routine quantitative assay on blood agar plates and a variant of LSU agar (medium 32)(Juhlin & Ericsson, 1961).

Isolated bacteria were identified with conventional biochemical tests (Cowan & Steel, 1970). In 90 of the total 96 patients (44 in the cefotaxime group and 46 in the control group) preoperative urinary culture and postoperative follow-up could be made for evaluation of bacteriuria. At 10 days and 6 weeks after TUR 82 patients (39 in the cefotaxime group and 43 in the control group) could be studied for bacteriuria. At 4 months the figures were 32 and 37 respectively.

Susceptibility testing: The sensitivity to antibiotics of the isolates was assessed immediately after isolation using a disc diffusion method (Ericsson & Scherris, 1971) on PDM antibiotic sensitivity medium agar (AB Biodisk, Stockholm). After the clinical study was completed the minimum inhibitory concentration (MIC-value) of the isolated bacteria was determined with an agar dilution method (Forsgren, 1981). The medium used was PDM agar and the inoculum consisted of a four-hour culture diluted in saline to a concentration of 10^{10} bacteria per litre and applied to the surface of the agar in 1 to 2 μ l quantities with the aid of a multipoint inoculator. Ampicillin (AS 360 Leo, Denmark) and cefotaxime (Hoechst 65) were tested. The evaluation of resistance and sensitivity respectively was based on the SIR-system (the Swedish reference group for antibiotics).

Comparability: The cefotaxime- and control groups were comparable in terms of operation procedure and postoperative care, frequency of malignancy and weight of the resected specimen and concomitant diseases. A just significant difference was observed in the mean age ($p = 0.03$) but there was no statistical significance regarding the period of hospitalization ($p = 0.1$) and the number of days of postoperative care ($p = 0.06$)(table I).

Statistical methods: Testing for significance was performed using the two-by-two Chi square test and the Fischer's exact test. Means were compared according to normal and t-distribution as required.

RESULTS

Bacteriuria: The frequency of bacteriuria in *all patients* preoperatively and in the early and late follow-up after TUR is presented in fig. 2. On admission (A) 48 per cent of the patients in the cefotaxime group and 63 per cent in the control group had bacteriuria. The day of discharge from the

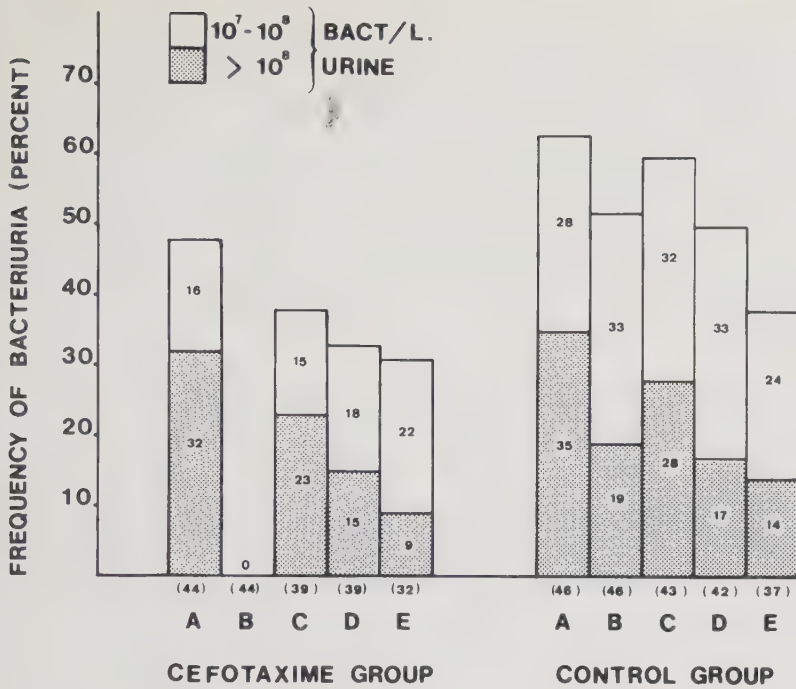


Fig 2. Frequency of bacteriuria in all patients of the cefotaxime and the control group. A - E = culture times as shown in Fig 1. Figures in brackets indicate the total of investigated patients.

Table II. Infectious and non-infectious complications within one week after TUR in 96 patients.

Complications	Cefotaxime group (n = 47)	Control group (n = 49)
Septicemia	2	2
Chill (negative blood culture)	1	0
Upper urinary tract infection	1	5
Lower urinary tract infection	0	1
Severe postoperative bleeding	2	5
Re-catheterization	4	4
Cardiovascular, respiratory	0	1
Others	2	4
Total	12	22 *
No of patients with complications	12	19

* ($p < 0.05$)

hospital (B) no patients in the cefotaxime group had bacteriuria whereas in the control group 52 per cent had bacteriuria. At 10 days (C) and six weeks (D) after TUR the frequencies of bacteriuria in the cefotaxime group were 38 per cent and 33 per cent respectively while in the control group they were 60 per cent and 50 per cent. Four months after TUR bacteriuria was still present in 31 per cent in the cefotaxime group and 38 per cent in the control group. The intergroup difference was not statistically significant except for at the day of discharge (culture B).

Out of 20 patients *without bacteriuria* preoperatively in the cefotaxime group with complete bacteriological follow-up, 17 (85 %) remained non-bacteriuric during the whole follow-up period. The remaining three patients acquired a non-significant bacterial count. In the control group 11 out of 17 preoperatively uninfected patients (65 %) remained non-bacteriuric. Four patients acquired significant and two non-significant bacteriuria. No statistical difference was observed between the cefotaxime group and the control group ($p > 0.1$).

Out of 21 *preoperatively bacteriuric* patients in the cefotaxime group bacteriuria recurred in 15 patients (14 with the same isolate and 1 with a new strain). Only four patients were cured from infection by the association of the operation and the short antimicrobial course. Data were missing in two patients. Thus the antibiotic course essentially failed to prevent the recurrence of preoperatively prevailing bacteriuria. In the control group 26 patients out of 29 showed postoperative bacteriuria. The same isolates persisted in 21 subjects and a new pathogen emerged in five. Three patients became non-bacteriuric postoperatively, two of them after an antibiotic treatment necessitated by clinical signs of upper urinary tract infection and one spontaneously.

Infectious complications: The infectious complications observed in the first week after TUR in 96 patients from both groups are presented in table II. There were two cases of *septicemia* in each group. In three patients *E. coli* was isolated in both the preoperative urine culture and the postoperative blood culture. In the fourth patient an enterobacteriaceae (*Citrobacter*) was observed preoperatively (urine) and directly postoperatively (blood). The sensitivity pattern pre- and postoperatively was identical in all cases. In two of the septicemic patients microscopic examination of the prostatic specimen revealed chronic inflammation. In one case a bladder stone was present in addition to hyperplasia of the prostate. *Upper urinary tract*

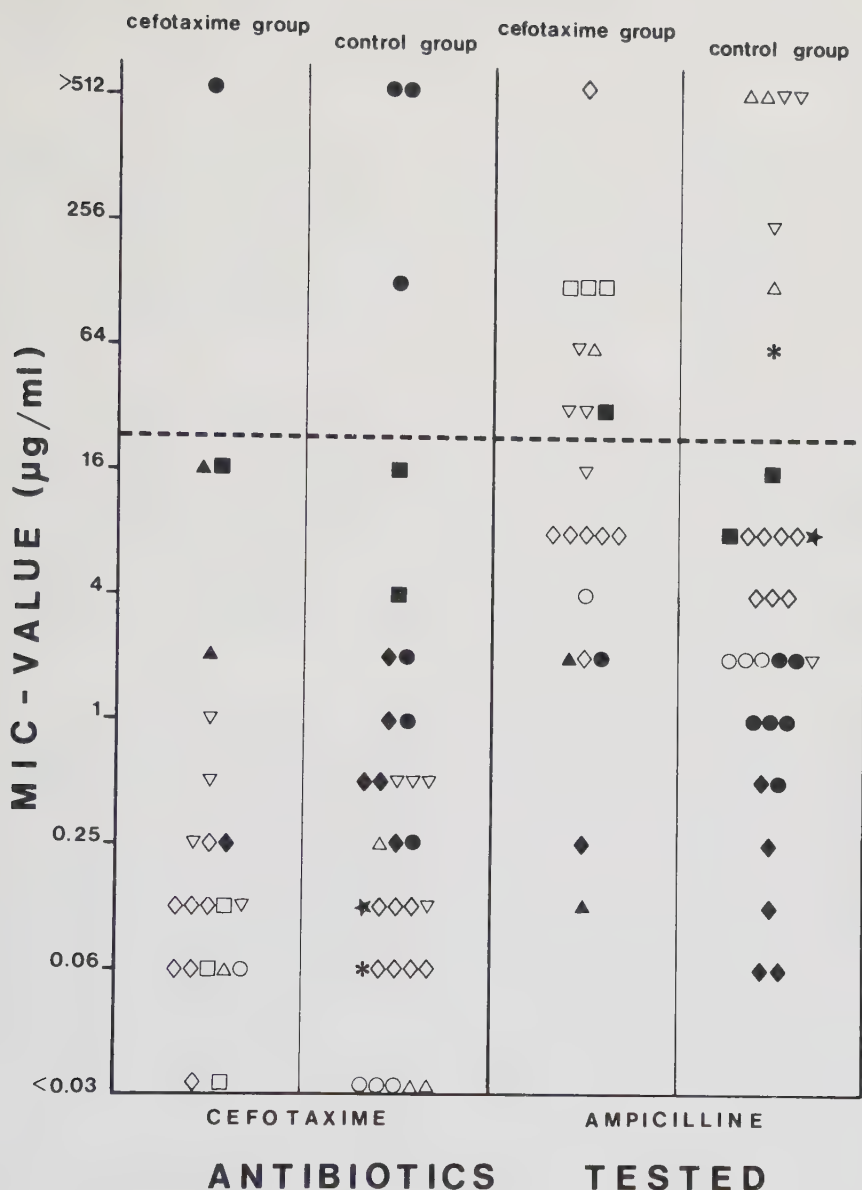


Fig 3. Preoperative bacterial isolates in the cefotaxime and the control group as tested for cefotaxime and ampicillin. Symbols above the dotted line indicate resistance to the drug according to the SIR system (the Swedish reference group for antibiotics). Four isolates were not available for analysis. Symbols: *E. coli* (◇); *Klebsiella* (□); *Enterobacter* (▽); *Proteus mirabilis* (○); other *Proteus* (△); *Citrobacter* (★); *Acinetobacter* (■); *Serratia* (*); *Enterococci* (●); *Staphylococcus epidermidis* (◆); *Staphylococcus aureus* (▲).

Table III. Bacterial isolates ($\geq 10^7$ cfu/l) from 90 patients (44 in the cefotaxime group and 46 in the control group) 1-3 days before TUR, recurring respectively persisting after surgery and acquired at any time until 6 weeks postoperatively in patients with negative urine culture preoperatively.

Species	Number of isolates					
	Cefotaxime group			Control group		
	Preoperative	Recurring	Acquired	Preoperative	Persisting	Acquired
<i>E. coli</i>	7	4	-	7	5	-
<i>Klebsiella</i>	3	2	-	-	-	-
<i>Enterobacter</i>	4	3	-	4	4	-
<i>Proteus mirabilis</i>	1	1	-	3	3	1
<i>Proteus morganii</i> , <i>vulgaris</i> , <i>rettegi</i>	1	1	-	3	3	-
<i>Citrobacter</i>	-	-	-	1	0	-
<i>Acinetobacter</i>	1	0	1	2	0	-
<i>Serratia</i>	-	-	-	1	1	-
<i>Enterococci</i>	1	0	-	6	3	2
<i>Staph. epidermidis</i>	3	1	2	6	1	3
<i>Staph. aureus</i>	2	2	-	1	1	-
Total bacteria	23	14	3	34	21	6
Total patients	21	14	3	29	21	6

infection was recorded in 6 patients, 5 in the control group and one in the cefotaxime group. With regard to the total number of infectious complications the groups are too small to give an intergroup statistical significance ($p > 0.1$).

All complications: Considering, in addition to the infectious events, other *postoperative complications* such as severe postoperative bleeding, the need for a prolonged period of catheterization and cardio-vascular complications there was a total of 12 complications in 12 patients in the cefotaxime group and 22 complications in 19 patients in the control group. The difference is statistically significant ($p < 0.05$).

Period of hospitalization: The patients in the control group were hospitalized an average of 8.5 days as compared to those in the cefotaxime group, 6.9 days ($p = 0.1$). The number of days from the operation to discharge from hospital was also greater in the control group (mean: 5.9 days) as compared to the cefotaxime group (mean: 4.4 days) ($p = 0.06$). The patients with severe infectious complications were hospitalized for a longer period of time (mean: 10.5 days).

Bacteriological findings: Table III illustrates the number of isolates in both groups. Preoperatively the intergroup distribution is very similar except for a larger amount of enterococci in the control group (6) as compared to the cefotaxime group (1). In the cefotaxime group 14 of the 23 preoperatively isolated bacteria strains recurred postoperatively and in the control group 21 of the 34 persisted. The isolates acquired postoperatively are also shown in table III. The minimal inhibitory concentration (MIC-value) for the preoperatively isolated bacteria is demonstrated in fig. 3. *In vitro* all strains except for four enterococci were sensitive to the drug used in the trial. Cefotaxime showed a higher degree of efficacy than ampicillin.

Side-effects: Cefotaxime was well tolerated and no side-effects due to the drug was registered during the trial.

DISCUSSION

In conjunction with transurethral resection of the prostate preoperatively bacteriuric patients remain bacteriuric in unchanged proportions. Preoperatively non-bacteriuric patients acquire bacteriuria in a significant rate (Plorde, Kennedy, Bourne, Ansell & Pettersdorf, 1965; Genster et al, 1970). Several recent investigations have demonstrated a reduction in the

postoperative frequency of bacteriuria and of the number of postoperative infectious complications (Williams et al; Hargreave et al; Grabe et al, 1984a) when antibiotics have been given to cover the operation and the early postoperative period, usually throughout the period of catheterization. The purpose of the present study was to clarify if a short antibiotic course given postoperatively at the time of and after the removal of the indwelling catheter, one of the sources of persisting and acquired infections, could effectively reduce the presence of postoperative bacteriuria. This schedule left the patients, bacteriuric or not at operation, unprotected and thus allowed to observe the development in the early postoperative period of complications in all patients and to initiate appropriate therapy if necessary.

In this study, *bacteriuria* was present preoperatively in 48 per cent in the cefotaxime and 63 per cent in the control group. On the day of discharge, i.e. usually one to two days after catheter removal, there was no bacteriuria at all in the cefotaxime group compared to half of the patients in the control group ($p < 0.001$). This can be explained by the high cefotaxime concentrations achieved in urine and by the bacteriostatic effect of the drug. But bacteriuria recurred within one week in the treated group and thereafter no statistical difference was observed between the groups regarding the incidence of bacteriuria. The regimen showed some efficacy in preventing preoperative non-bacteriuric patients from acquiring bacteriuria but there was no significant intergroup difference. The study failed to demonstrate a therapeutic effect by reducing the frequency of bacteriuria in preoperatively infected patients. Thus such a scheduled course had no impact in the long term on the frequency of bacteriuria and must be considered either to be too short a course to eradicate bacteriuria or to be administered at an inappropriate period in elderly newly prostatectomized men.

Septicemia arising within the first 24 hours, was observed in four patients (4%), two in each group. *Upper urinary tract infection* was seen in only one patient in the cefotaxime group while five appeared in the control group (6%). The intergroup difference may indicate that an early inset of the antimicrobial agent can prevent involvement of the upper urinary tract. These results are strikingly different from those observed in a study mentioned earlier (Grabe et al, 1984a) in which the antimicrobial agent was scheduled to cover the operation as well as the immediate postoperative period and where almost no infectious complications were recorded. This observation suggests that the antibiotics should be administered perioperatively to obtain adequate serum

and tissue concentration of the drug during and directly after the operation to counteract the establishment of an infection. Further support to this observation is found in other studies (Williams et al, Hargreave et al, Ramsey et al).

Although the number of patients in the present study was limited, the total number of *complications* was significantly lower in the antibiotic group as compared to the control group. The patients with infectious complications stayed longer in the hospital. We also found that the subjects not given the antibiotic remained longer in hospital which can be explained on the one hand by the higher number of complications and on the other hand by the intergroup difference in age and presence of cancer of the prostate and the resulting therapeutic and social issues.

The *pathogens* isolated preoperatively were evenly distributed and comparable to findings from earlier years in the same hospital (Grabe, Forsgren & Hellsten, 1984b). Gram-negative species predominated but Gram-positive species, mainly enterococci and *Staphylococcus epidermidis* were frequently encountered, a pattern also described by others (William and Hole, 1982). The susceptibility testing demonstrated the higher efficacy *in vitro* of cefotaxime compared to such a commonly used antibiotic as ampicillin. At the time of this trial cefotaxime had been used for more than two years in our department for prophylaxis in controlled clinical trials and for the treatment of patients with severe urinary tract infections including systemic infections like septicemia originating in the urinary tract. No modification of the species distribution was observed during this period and the sensitivity pattern of the isolated bacteria remained unchanged for cefotaxime as compared with those recorded in our previous trial (Grabe et al, 1984b). This observation supports the opinion that short scheduled antibiotic courses do imply a low risk of development of resistance to the drug.

We know of no comparable studies to confirm our results. Our data emphasize the importance of antibiotics in patients undergoing TUR mainly by keeping non-bacteriuric patients uninfected postoperatively and by preventing the development of postoperative upper urinary tract infections within the first week. But the short course essentially failed to reduce the postoperative frequency of bacteriuria, and had no therapeutic effect in preoperatively bacteriuric patients. Furthermore 10 per cent of serious postoperative infectious complications were observed during the trial.

We therefore conclude that such a designed postoperative antibiotic course is a less effective alternative to give patients undergoing TUR than the one scheduled to administer the antimicrobial agent perioperatively.

REFERENCES

- Berger, S.A. & Nagar, H. 1978. Antimicrobial prophylaxis in urology. *J Urol*, 120, 319 - 322.
- Chodak, G.W. & Plaut, M.E. 1979. Systemic antibiotics for prophylaxis in urologic surgery: A critical review. *J Urol*, 121, 695 - 699.
- Cowan, S.T. & Steel, K.J. Manual for the identification of medical bacteria. Cambridge University Press, London, 1970.
- Ericsson, H.M. & Sherris, J.C. 1971. Antibiotic sensitivity testing. Report of an international collaborative study. *Acta Pathol Microbiol Scand (B) Suppl*, No. 217.
- Forsgren, A. 1981. Comparative in vitro activity of first and second generation cephalosporin. *Acta Pathol Microbiol Scand (B)*, 89, 221.
- Genster, H.G. & Madsen, P.O. 1970. Urinary tract infections following transurethral prostatectomy: With special reference to the use of antimicrobials. *J Urol*, 104, 163 - 168.
- Grabe, M., Forsgren, A. & Hellsten, S. 1984a. The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*, in press.
- Grabe, M., Forsgren, A. & Hellsten, S. 1984b. Species distribution and antibiotic sensitivity of bacteria isolated pre- and postoperatively from patients undergoing transurethral prostatic resection. *Scand J Urol Nephrol*, in press.
- Hargreave, T.B., Hindmarsh, J.R., Elton, R., Chisholm, G.D. & Gould, J.C. 1982. Short-term prophylaxis with cefotaxime for prostatic surgery. *Br Med J*, 284, 1008 - 1010.
- Juhlin, I. & Ericsson, C. 1961. A new medium for bacteriological examination of stools (LSU-Agar). *Acta Pathol Microbiol Scand*, 52, 185 - 199.
- Plorde, J.J., Kennedy, R.P., Bourne, H.H., Ansell, J.S. & Pettersdorf, R.G. 1965. Course and prognosis of prostatectomy: With a note on the incidence of bacteriuria and effectiveness of chemoprophylaxis. *N Engl J Med*, 272 (6), 269 - 277.
- Ramsay, E.W. & Sheth, N.K. 1983. Antibiotic prophylaxis in patients undergoing prostatectomy. *Urol*, 22, 376 - 378.
- The Swedish reference group for antibiotics. A revised system for antibiotic sensitivity. *Scand J Inf Dis*: 13: 148 - 152. (1981).
- Williams, M., Hole, D.J., Murdoch, R.W.G., Ogden, A.C. & Hargreave, T.B. 1980. 48-hour cephradine and postprostatectomy bacteriuria. *Br J Urol*, 52, 311 - 315.
- Williams, M. & Hole, D.J. 1982. Bacteriuria in patients undergoing prostatectomy. *J of Cl Pathol*, 35, 1185 - 1189.

IV

LONG-TERM FOLLOW-UP AFTER TRANSURETHRAL PROSTATIC
RESECTION WITH OR WITHOUT A SHORT PERIOPERATIVE
ANTIBIOTIC COURSE.

M. Grabe & S. Hellsten

ABSTRACT

This study was undertaken to analyse the outcome of 192 patients who three to four years earlier had undergone TUR in a controlled clinical trial aimed to investigate the value of a short perioperative antibiotic course. The survival rate was comparable in both groups and no mortality attributable to infectious events secondary to urological disease was observed. Most deaths were due to cardiovascular disease and/or cancer of the prostate and of the gastrointestinal tract. Infectious events predominated in the control group and more antibiotics were prescribed to the patients in the same group during the whole follow-up compared to the patients in the perioperative antibiotic group. Bacteriuria was found at follow-up control in 24 per cent of the patients, evenly distributed between the groups. Eighty-three per cent of the patients were satisfied with the results of prostatectomy but 41 per cent complained of symptoms from the lower urinary tract. No influence on the maximum urinary flow rate was observed in bacteriuric patients or individuals with symptoms. No intergroup difference was found regarding mortality or morbidity except for the frequency of postoperative urethral stricture formation that was significantly higher in the controls. We concluded that prospective long-term follow-ups are indicated to evaluate the impact of short perioperative antibiotic courses even regarding the long-term morbidity.

INTRODUCTION

Transurethral resection (TUR) has replaced open surgery in most instances of obstruction due to prostatic enlargement. The advantages over open surgery are lower mortality and morbidity, less discomfort for the patients and shorter hospitalization period. Earlier reports have focused on complications such as postoperative mortality and morbidity and long-term complications such as incontinence, epididymitis and urethral stricture (Davis, 1931; Holtgrewe & Valk, 1964; Bandhauer & Madersbacher, 1969; Singh, Tresidder & Blandy, 1973; Melchior, Valk, Forest & Mebust, 1974; Obrant, 1976; Lund & Dingsør, 1976; Chilton, Morgan, England, Paris & Blandy, 1978). In the present investigation we reviewed the outcome of 192 patients who underwent TUR and were enrolled in a controlled clinical trial that started four years earlier. The aim of the initial clinical trial was to evaluate the effects of a short antibiotic course in TUR on early postoperative infectious complications and bacteriuria. These were found to be significantly reduced by such a scheduled course compared to an untreated control group. The clinical results have been presented in a previous report (Grabe, Forsgren & Hellsten, 1984a) as have been the bacteriological findings (Grabe, Forsgren & Hellsten, 1984b). The aim of the present study was to determine by the means of a retrospective analysis whether a short perioperative antibiotic course had any impact on the long-term mortality and morbidity, with focus on survival rate, the infectious events and related long-term complications and the patients' appraisal of the results of operation.

MATERIAL AND METHODS

The patients: During one year starting on March 15th, 1978, 192 patients, who were to undergo transurethral prostatic resection were enrolled in a prospective trial. Patients with hypersensitivity to penicillin or cephalosporins, patients who had received antibiotics during the week before TUR and those with serum creatinine higher than $115 \mu\text{mol/l}$ had been excluded from the study. 98 patients were randomized to receive a potent antibiotic (cefotaxime) administered from the day before the operation to the day of removal of the postoperatively inserted catheter. 94 patients were assigned to a control group without antibiotics. The mean age of the patients at the time of operation was 71 years. The two groups were comparable in terms of age, preoperative catheter treatment and prevalence of bacteriuria, operative procedure and postoperative care, concomitant diseases and weight of and malignancy in the resected specimen. Four years after the trial started all patients' case records were reviewed. The patients were asked to answer a questionnaire. A urine sample for culture was collected and a uroflowmetry

was made in most cases. The primary cause of death as indicated in the autopsy records (26) and death certificates (15) was examined in the patients who had died during the observation period.

At the reckoning day four years after the trial started 41 out of 192 patients had died. Of the 151 patients alive 19 could not participate because they were seriously ill (3), had moved to another town (4) or could not be reached (12). A questionnaire was sent to the remaining 132 patients, 110 of whom answered most of the questions. Twenty-two patients did not co-operate either because of serious disease (8) or refused even after personal contact (14).

The questionnaire: The patients were asked: .

- if their voiding after the operation: a) was much improved, b) improved, c) remained unchanged, d) became worse.
- if they had any remaining symptoms from the lower urinary tract such as a) pain when passing urine, b) frequency, c) terminal dribbling, d) poor stream, e) turbid and/or ill-smelling urine.
- about the frequency of voiding during night time before and after TUR.
- if they had been prescribed any antibiotics during the observation period.

Uroflowmetry: All patients answering the questionnaire were asked to carry out a uroflowmetry which was done with a DISA mictiograph (21F05). The maximum flow rate and the voided volume were considered.

Urine culture: A clean mid-stream urine sample was collected for urine culture and the incubation time was four hours when possible. The samples were immediately refrigerated and bacteriological processing usually began within 1 - 2 hours. Cultures were run with routine quantitative assay on blood agar plates and on a variant of LSU (medium 32) agar (Juhlin & Ericsson, 1961). Isolated bacteria were identified with conventional biochemical tests (Cowan & Steel, 1970) and their sensitivity to antibiotics was assessed with a disc diffusion method (Ericsson & Sherris, 1971) on PDM antibiotic sensitivity medium agar (AB Biodisk, Stockholm). Non-significant bacteriuria was defined as 10^7 - 10^8 colony forming units per litre (cfu/l) and significant bacteriuria in the presence of $>10^8$ cfu per litre.

Definitions: All diagnoses were made on a clinical basis, as described before (Grabe et al, 1984a). Septicemia was defined as positive blood culture with high fever and systemic symptoms. Upper urinary tract infection (UTI) was diagnosed as fever associated with flank pain and/or systemic symptoms and

positive urine culture. Lower UTI was defined as symptoms of cystitis with positive urine culture. Chronic bacteriuria was recorded when bacteriuria recurred in spite of several discrete antibiotic courses. Stricture of the meatus or other parts of the urethra and of the bladder neck was suspected when the patients complained of a poor urinary stream with or without lower urinary tract symptoms. The diagnosis was made by a typical uroflowmetry curve and confirmed by inspection, urethrocystoscopy or urethrocystography. A stricture was defined as a narrowing of the urethra requiring surgical treatment.

RESULTS

Mortality: Forty-one patients (21%) died during the follow-up period. Mortality during the first month, the remaining part of the first year and each consecutive year after TUR up to the fourth year is presented in Table I. The primary cause of death as indicated on death certificate or autopsy record is reported. Three patients died within the first month one of acute cardiac failure, one of septicemia, cardiac failure and severe postoperative bleeding and one of metastasizing rectal cancer. The patient with septicemia, who belonged to the control group, was the only fatal case directly attributable to infectious complication following TUR. Acute and chronic cardiovascular disease (including pulmonary embolism) caused the largest number of deaths (18). Prostatic cancer with metastases (11) and other cancers (8), mainly gastrointestinal caused a similar number of deaths. Severe pneumonia (3) and one case of advanced kidney failure were further causes of death. In most patients a combination of cardiovascular and malignant disease was observed. At the time of death, the mean age of these patients was 75 years. Twenty patients belonged to the cefotaxime group and 21 to the control group.

Morbidity: The postoperative complications occurring up to 6 weeks are presented elsewhere (Grabe et al, 1984a). A statistical significant intergroup difference regarding the two severe infectious complications (septicemia and upper UTI) and reduction in the frequency of postoperative bacteriuria was observed. Table II shows the infectious episodes and complications observed six weeks to three months and after three months in both groups respectively. There was a predominance of infectious events in the control group compared to the antibiotic group. Septicemia occurred in two patients, in one due to calculous pyelonephritis and in the other after urethral instrumentation for stricture of the urethra, this patient not being covered by an antibiotic. Upper urinary tract infection was recorded in four patients and could be related to predisposing factors such as pelvic stones in two patients and recurrent UTI in one diabetic patient. The fourth case followed a revision TUR due to obstruction

Table I. Number and cause of death in 192 patients. Mean follow-up 3.5 years.

Time of death	No of death	Alive (percent)	Cause of death			
			Cardiovascular disease	Cancer of prostate	Other cancer	Respiratory or renal disease
< 1 month	3	98.4	2*	-	1	-
1 month - 1 year	7	94.8	4	2	1	-
1 - 2 years	8	90.6	3	4	1	-
2 - 3 years	17	81.8	5	5	3	4
3 - 4 years	6	78.6	4	-	2	-
Total	41	78.6	18	11	8	4

* one case of acute heart failure; one case of septicemia, severe bleeding and cardiac failure.

Table II. Infectious events and stricture of the urethra observed between 6 weeks - 3 months and after 3 months after TUR in 192 patients (98 in the cefotaxime group and 94 in the control group).

Diagnosis	6 weeks - 3 months cefotaxime group	control group	after 3 months cefotaxime group	control group
Infections				
Septicemia	-	-	1	1
Upper UTI	-	-	1	3
Lower UTI	6	13	7	12
Epididymitis	1	-	-	1
Chronic bacteriuria	-	-	4	7
Stricture				
Meatus	-	-	1	3
Urethra (other parts)	-	-	-	4
Bladder neck	-	-	1	3

Table III. Clinical features in 12 patients with stricture of the urethra compared to all patients.

Clinical feature	Patients with stricture (n=12)	All patients (n=192)
Age, years (mean)	66.0	71.3
% with indwelling catheter before TUR	33	37
% with preoperative bacteriuria	41	42
% with postoperative bacteriuria	58	16 - 54*
% with prostatic cancer	25	24
Weight of the resected specimen (g, mean)	7.0	15.8
Hospitalization, days (mean)	9.4	7.4

* in the cefotaxime and the control group respectively, at 10 days control after TUR.

Table IV. Instrumentation and endoscopic operation on 192 patients after TUR.
Mean follow-up 3.5 years.

Instrumentation/ Operation	cefotaxime group	control group
Cystoscopy	9	7
Revision TUR / bladder neck incision	5	4
Open bladder neck reconstruction	0	3
Lithotripsy	1	0

from residual tissue. The number of lower UTI was slightly higher in the control group (12) than in the cefotaxime group (7). This was also the case for chronic recurrent bacteriuria diagnosed in seven cases in the former and four in the latter group respectively. Antibiotics were prescribed to a higher number of patients in the control group (22) than in the cefotaxime group (13) during the whole period as far as could be registered through the case records and the questionnaire.

Bacteriuria: At the follow-up examination, bacteriuria was displayed in 24/100 patients, 14 in the cefotaxime group and 10 in the controls. Five of these were significant bacteriuria and 19 non-significant. The Gram-negative species predominated largely (27/29 isolated strains). The proportion of patients with preoperative permanent catheter (37%), bacteriuria (46%) or carcinoma of the prostate (21%) did not differ markedly from the rates in all patients. No overrepresentation of predisposing factors such as urinary tract stone (one patient) or bladder cancer (2) was found in these patients.

Stricture of the urethra or bladder neck: Postoperative stricture of the urethra or bladder neck was observed in twelve patients (table II), two of them in the cefotaxime group and ten in the control group ($p = 0.03$). Four of the strictures were soft narrowing of the external meatus, two of which were known before TUR, and treated by simple repeated dilatations. Even after exclusion of the four meatal strictures, a just significant intergroup difference was recorded ($p = 0.05$). Of the four patients with stricture of other parts of the urethra one received a permanent perineal urethrostomy and one was treated by dilatations. Two patients were offered surgical treatment but refused and remained with poor stream. Three of the bladder neck obstructions were operated on by bladder neck reconstruction and one by transurethral bladder neck incision. The clinical features in the patients with stricture formation are compared to the total material in table III. The patients with stricture were younger (mean age at TUR: 66 years) and the weight of the resected prostate was lower (mean: 7 g) than the average in all patients (71 years and 16 g respectively). Three out of 12 (25%) patients with stricture had bacteriuria in the follow-up urine culture, i.e. the same proportion as in the total material.

Instrumentation and operations: Four patients in each group underwent a second TUR for benign or malignant residual glandular tissue. Sixteen patients evenly distributed between the two groups were subjected to urethrocystoscopy one or several times for bladder cancer control or endoscopic diagnosis. Lithotripsy was carried out on one patient for a remaining bladder stone (table IV).

Patients' appraisal: The patients' own opinion regarding the results of prostatectomy three to four years after TUR is presented in table V and is shown to be similar in both groups. Eighty-eight patients (83%) were satisfied with the results of the operation. Sixty-three patients (59%) had no remaining symptoms whereas 43 (41%) complained of one or more of the symptoms from the lower urinary tract as displayed in table VI. Bacteriuria was found in the same proportion of patients with symptoms (23%) as without (24%). Twenty out of twenty-four (83%) patients with bacteriuria were also satisfied, but almost all (96%) complained of frequency or pain when passing urine. In contrast only 34 per cent of the non-bacteriuric patients reported symptoms ($p < 0.001$). Three patients complained of incontinence. The frequency of night time voiding before and after operation as reported by the patients is illustrated in figure 1. A significant reduction in the frequency was demonstrated postoperatively ($p < 0.01$).

Uroflowmetry: Ninety-three patients carried out uroflowmetry with a voided urine volume of ≥ 100 ml, 67 of whom with a volume ≥ 150 ml. The mean maximum flow rate was 14.5 ml per second (range 2 - 25) and the distribution is presented in figure 2. Thirty patients had a maximum flow over 15 ml per second. The figure for the patients complaining of lower urinary tract symptoms was 13.3 ml per second compared to 15.4 in patients without symptoms. Bacteriuric patients had a mean maximum flow of 14.0 ml per second. The intergroup distribution was fully symmetric and no statistical difference was found in any of the comparisons.

DISCUSSION

In a previous study we demonstrated the efficacy of a short perioperative antimicrobial course with cefotaxime to reduce the frequency of infectious complications and bacteriuria (Grabe et al, 1984a). In the present retrospective review we analysed the outcome of the patients up to an average of 3.5 years after TUR in an attempt to assess the value of a short antibiotic course on the morbidity and mortality whether due to infections or not.

Late mortality during the follow-up time could be ascribed to either cardiovascular or malignant disease, mainly cancer of the prostate and of the gastro-intestinal tract. No intergroup difference was found. Although no fatal infectious episodes arose during the period of observation there were two severe infectious complications to endoscopic procedure in patients without appropriate antibiotic cover. These events underline the value of a short adequate antibiotic course in conjunction with such urological

Table V. The patients' appraisal of TUR. Mean follow-up 3.5 years.
(106 answers).

	cefotaxime group	control group	total	percent
Much improved	32	20	52	49
Improved	15	21	36	34
No change	4	7	11	10
Worse	4	3	7	7

Table VI. Remaining symptoms as expressed by 106 patients. Mean follow-up
3.5 years.

Symptoms	cefotaxime group (n=56)	control group (n=50)	total	percent
No symptoms	37	26	63	59%
Symptoms*	19	24	43	41%
painful voiding	2	5	7	
frequency	4	11	15	
terminal dribbling	7	7	14	
poor stream	8	10	18	
turbid and/or ill smelling urine	5	8	13	

* > one symptom in some patients.

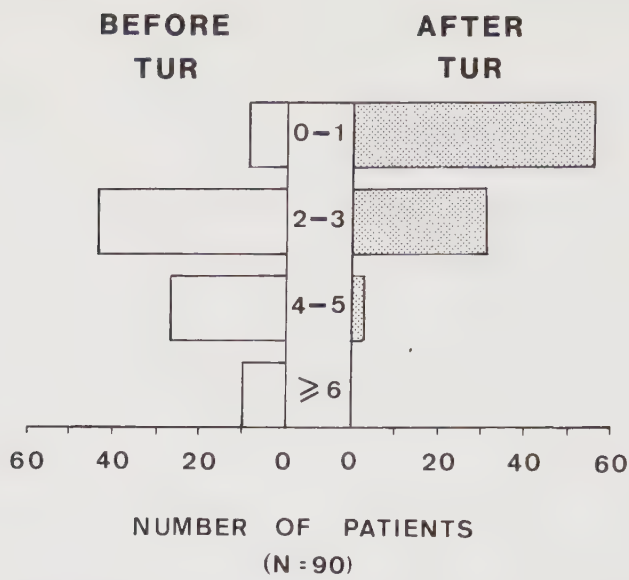


Fig 1. Frequency of voiding during night time in 90 patients before and 3-4 years after TUR. The figures in the central area express the frequency of micturition.

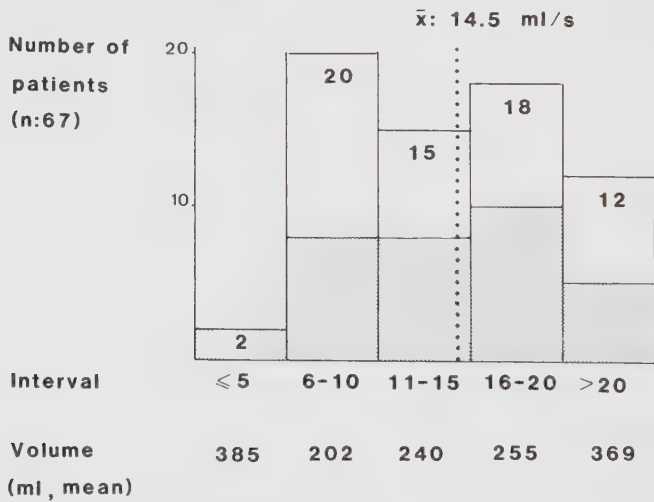


Fig 2. Distribution of maximum flow rates obtained 3-4 years after TUR from 67 patients, 33 from the control group (dotted area) and 34 from the cefotaxime group (white area). The figures within the bars represent the total number of patients for each flow rate interval. The lowest row indicates the mean voided volume for the patients in each interval. The mean maximum flow rate for all patients was 14.5 ml/s.

manipulations, at least in bacteriuric patients as previously pointed out for patients undergoing TUR (Williams, Hole, Murdoch, Ogden & Hargreave, 1980; Hargreave, Hindmarsh, Elton, Chisholm & Gould, 1982; Grabe et al, 1984a) or other urological instrumentations (Korbel & Maher, 1976).

Infectious episodes predominated in patients belonging to the control group as compared to those who received cefotaxime perioperatively. It is also worth mentioning that a higher number of patients in the control group were prescribed antibacterial agents during the first three months postoperatively as well as later. Bacteriuria was found in 24 per cent of the patients at the late follow-up after TUR. No causal factor to bacteriuria could be defined. It is known that the prevalence of bacteriuria increases with age and may be explained by changes in bladder function, prostate gland size, immunologic status and concomitant disease (Freedman, 1983). This is particularly true for elderly institutionalized men as recently described by Nicolle (Nicolle, Bjornson, Harding & MacDonell, 1983). Our study, concerned with prostatectomized men, confirm the high prevalence of bacteriuria within this group of elderly men (mean age 75 years). A perioperative antibiotic course did not influence the long-term outcome regarding bacteriuria.

Most patients (83%) were satisfied with the outcome of the operation which is in accordance with the findings of Chilton et al. Nevertheless as many as 41 per cent reported one or more symptoms related to the lower urinary tract, but symptoms could not be correlated to bacteriuria. Almost all bacteriuric patients (96%) complained of symptoms mainly in terms of frequency and painful voiding but without influencing their positive evaluation of the results of the TUR. On the other hand non-bacteriuric patients reported symptoms in only 34 per cent. Neither lower urinary tract symptoms nor presence of bacteriuria could be related to significant reduced maximum urinary flow rate.

Urethral stricture formation was found postoperatively in 12 patients. All strictures were attributed to TUR except for two meatal ones that were known prior to TUR. Ten of the strictures were observed in the control group in contrast to only two in the cefotaxime group ($p < 0.05$). A treatment from simple dilatation to open bladder neck reconstruction was required in 10 patients. Many reasons for postoperative stricture formation have been discussed such as insufficient preoperative calibration of the urethra, too large instruments, lengthy resections and urinary tract infections (Holtgrewe et al; Madersbacher & Marberger, 1971; Lentz, Mebust, Foret & Melchior, 1977). Both Robinson and Holtgrewe found that low weight of the resected prostatic

specimen was a common feature in bladder neck stricture (Robinson & Greene, 1962; Holtgrewe et al). This was also the case in our study. The patients with stricture formation followed the same pattern concerning the frequency of pre- and postoperative bacteriuria as those in the control group. However, our limited study does not allow us to identify bacteriuria as a specific causal factor. This is consistent with the findings of Hart who in a prospective study failed to prove any increased frequency of urethral stricture in bacteriuric patients (Hart & Fowler, 1981). Nevertheless our findings in terms of a difference between the antibiotic- and the control group suggest an interrelationship between stricture formation and infectious events.

In the long-term follow-up of patients undergoing TUR we did not find any late mortality attributed to infectious events. However a higher morbidity in terms of infectious episodes was recorded in patients without any antibiotic cover during TUR as compared to patients receiving antibiotics perioperatively. The frequency of postoperative urethra stricture formation was significantly higher in the control group. It is therefore concluded that prospective long-term scheduled follow-ups are prerequisite to assess the risk of infectious events and stricture formation in patients with or without antibiotic cover at the time of TUR.

Acknowledgments:

We are sincerely indebted to *Christina Gullstrand* for invaluable assistance with secretarial work and data collection and to *Ann-Cathrin Werther* for devoted handling of medical records.

REFERENCES

- Bandhauer, K., Madersbacher, H. 1969. Früh- und Spätkomplikationen transurethraler Eingriffe an der Prostata. *Der Urologe*, 8. Jahrgang, Heft 2, 48, 50 - 57.
- Chilton, C.P., Morgan, R.J., England, H.R., Paris, A.M.I. & Blandy, J.P. 1978. A critical evaluation of the results of transurethral resection of the prostate. *Br J Urol*, 50, 542 - 546.
- Cowan, S.T. & Steel, K.J. 1970. *Manual for the identification of medical bacteria*. Cambridge University Press, London.
- Davis, T.M. 1931. Prostate operation. Prospects of the patient with prostatic disease in prostatectomy vs. resection. *J.A.M.A.*, 97, 1674 - 1679.
- Ericsson, H.M. & Sherris, J.C. 1971. Antibiotic sensitivity testing. Report of an international collaborative study. *Acta Pathol Microbiol Scand (B)*, Suppl 217.
- Freedman, L.R. 1983. Urinary-tract infections in the elderly. *N Engl J Med* 1983; 309: 1451 - 1452.
- Grabe, M., Forsgren, A., Hellsten, S. 1984a. The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*. In press.
- Grabe, M., Forsgren, A. & Hellsten, S. 1984b. Species distribution and antibiotic sensitivity of bacteria isolated pre- and postoperatively from patients undergoing transurethral prostatic resection. *Scand J Urol Nephrol*. In press.
- Hargreave, T.B., Hindmarsh, J.R., Elton, R., Chisholm, G.D. & Gould, J.C. 1982. Short-term prophylaxis with cefotaxime for prostatic surgery. *Br Med J*, 284, 1008 - 1010.
- Hart, A.J.L. & Fowler, J.W. 1981. Incidence of urethral stricture after transurethral resection of prostate. *Urol*, XVIII (6), 588 - 591.
- Holtgrewe, H.L. & Valk, W.L. 1964. Late results of transurethral prostatectomy. *J Urol*, 92, 51 - 55.
- Juhlin, I. & Ericson, C. 1961. A new medium for the bacteriological examination of stools (LSU-Agar). *Acta Pathol Microbiol Scand* 52, 185.
- Korbel, E.I. & Maher, P.O. 1976. Use of prophylactic antibiotics in urethral instrumentation. *J Urol*, 116, 744 - 746.
- Lentz, Jr., H.C., Mebust, W.K., Foret, J.D., Melchior, J. 1977. Urethral strictures following transurethral prostatectomy: Review of 2,223 resections. *J Urol*, 117, 194 - 196.
- Lund, B.L., Dingsør, E. 1976. Benign obstructive prostatic enlargement. *Scand J Urol Nephrol*, 10, 33 - 38.
- Madersbacher, H., Marberger, H. 1971. Zur Harnröhrenstriktur nach transurethralen Operationen. *Urologe*, 10. Jahrgang, Heft 2, 66 - 67.

Melchior, J., Valk, W.L., Foret, J.D. & Mebust, W.K. 1974. Transurethral prostatectomy: Computerized analysis of 2,223 consecutive cases. J Urol, 112, 634 - 642.

Nicolle, L.E., Bjornson, J., Harding, G.K.M. & MacDonell, J.A. 1983. Bacteriuria in elderly institutionalized men. N Engl J Med, 309, 1420 - 1425.

Obrant, K.O. 1976. Transurethral electroresection of prostatic adenoma. Scand J Urol Nephrol, 10, 26 - 32.

Robinson, H.P. & Greene, L.F. 1962. Postoperative contracture of the vesical neck. I. Review of cases and proposed theory of etiology. J Urol, 87, 601 - 609.

Singh, M., Tresidder, G.C. & Blandy, J.P. 1973. The evaluation of transurethral resection for benign enlargement of the prostate. Br J Urol, 45, 93 - 102.

Williams, M., Hole, D.J., Murdoch, W.G., Ogden, A.C. & Hargreave, T.B. 1980. 48-hour cephradine and postprostatectomy bacteriuria. Br J Urol, 52, 311 - 315.

CONCENTRATION OF CEFOTAXIME IN SERUM, URINE AND
TISSUES OF UROLOGICAL PATIENTS.

M. Grabe, K.-E. Andersson, A. Forsgren & S. Hellsten

M. Grabe, K.-E. Andersson, A. Forsgren, S. Hellsten

Concentrations of Cefotaxime in Serum, Urine and Tissues of Urological Patients

Summary: Following the injection of 1 g of cefotaxime i. m., the concentration in serum was analysed in 11 patients using a biological method. The standard elimination curve obtained was representative for a group of elderly men (mean age 71 years). Samples from seven patients were analysed simultaneously using the biological method and high pressure liquid chromatography; the results were comparable. In four patients the concentration of cefotaxime in the urine was determined; very high levels of the drug were found (mean concentration 3395 µg/ml at two hours and 1210 µg/ml at five hours). 66% of the drug was found to have been eliminated in the urine at five hours.

Cefotaxime penetrated the prostatic tissue, giving concentrations ranging from 1.2 to 3.8 µg/g between the first and third hour after the injection of 1 g i. m. In the kidney tissue the drug was detected in the cortex, the middle part of the parenchyma and the inner medulla, at concentrations of 4.1, 4.2 and 6.2 µg/g, respectively. The concentrations obtained in the serum, in urine, and in the prostate and kidney indicate that cefotaxime is a valuable drug for the treatment of urinary tract infections.

Zusammenfassung: Konzentration von Cefotaxim in Serum, Urin und Gewebe von urologischen Patienten. Die Konzentration von Cefotaxim im Serum wurde bei 11 Patienten nach intramuskulärer Injektion von 1 g Cefotaxim mit Hilfe einer biologischen Methode bestimmt. Die erhaltene Standard-Eliminationskurve ist für eine Gruppe von älteren Männern (mittleres Alter 71 Jahre) repräsentativ. Proben von sieben Patienten wurden gleichzeitig mit der biologischen Methode und Hochdruck-Flüssigkeitschromatographie untersucht, die Ergebnisse waren vergleichbar. Die Untersuchung der Cefotaxim-Urinkonzentrationen bei vier Patienten ergab sehr hohe Spiegel der Substanz (mittlere Konzentration nach zwei Stunden 3395 µg/ml, nach fünf Stunden 1210 µg/ml). 66% der Substanz fanden sich nach fünf Stunden im Urin wieder. Cefotaxim penetrierte in das Drüsengewebe der Prostata; die erreichten Konzentrationen lagen zwischen 1,2 und 3,8 µg/g zwischen der ersten und dritten Stunde nach Injektion von 1 g i. m. Im Nierengewebe wurde die Substanz in der Rinde, in den mittleren Parenchymanteilen und im inneren

Bereich der Markzone in Konzentrationen von 4,1, 4,2 und 6,2 µg/g gefunden. Die im Serum, Urin, in der Prostata und in der Niere gemessenen Konzentrationen zeigen, daß Cefotaxim ein wertvolles Medikament zur Behandlung von Harnwegsinfektionen ist.

Introduction

Cefotaxime (HR 756/Hoechst) is a new semi-synthetic, highly active cephalosporin for parenteral administration (1, 2). Its activity covers a wide range of pathogenic organisms including beta-lactamase producing enterobacteriae (3, 4, 5). An important property of the drug is its activity against pathogens, often considered as "problem" organisms in hospital practice, such as *Serratia marcescens*, *Klebsiella* and to some extent *Pseudomonas aeruginosa* (6, 7, 8). *In vitro* cefotaxime has been shown to be more active than penicillin and other cephalosporins, including new cephalosporins such as cefuroxime and cefoxitin, against most urinary tract pathogens (9, 10, 11, 12).

The present study was undertaken to investigate the tissue distribution of cefotaxime in patients subjected to transurethral resection of the prostate. The concentrations in serum, urine and prostatic tissue were determined. Moreover, the tissue concentration of cefotaxime in normal renal parenchyma was studied in patients undergoing nephrectomy due to renal malignancy.

Materials and Methods

Patients: Ten patients aged 61 to 82 years (mean 69 years) were selected to have the concentrations of cefotaxime in serum, urine and prostate analysed. From another 12 patients aged 59 to 85 years (mean 71 years) receiving the drug, the concentration in prostatic tissue and the concentration in a single blood sample taken simultaneously were determined. In six patients aged 22 to 73 years (mean 58 years) admitted for upper urinary tract malignancy and treated with cefotaxime, the concentration

Received: 18 December 1980

Dr. M. Grabe, Asst. Prof. S. Hellsten, Department of Urology, Malmö General Hospital, S-214 01 Malmö, Sweden;
Prof. K.-E. Andersson, Department of Clinical Pharmacology, University of Lund, S-221 01 Lund, Sweden;
Prof. A. Forsgren, Department of Clinical Bacteriology, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden.

in normal renal parenchyma was analysed. A single blood sample was taken when the renal artery was ligated.

On the day of admission, red and white blood cell and thrombocyte counts were performed and the blood concentration of hemoglobin, sodium, potassium, creatinine, urea, bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase determined. These analyses were repeated during the treatment with cefotaxime and one week after the patients had been discharged from hospital.

Treatment: The treatment schedule was the same for all patients. 1 g of cefotaxime was administered intramuscularly on the day before the operation. The second dose was given together with the preoperative medication, and thereafter 1 g was administered daily until the indwelling urethral catheter had been removed, usually on the second or third postoperative day. The six patients who had undergone nephrectomy received the treatment for five days following the operation.

Sampling schedule: On the day before the operation blood samples were collected at 0.5, 1.0, 2.0, 2.5, 3.0, 5.0, 9.0, and 24 hours. Urine was collected in four separate samples at 2.0, 3.0, 5.0 and 24 hours after the injection.

During the initial phase of the transurethral resection, specimens of prostatic tissue (3 to 4 g) were taken for the study. In 12 patients samples from the outer layer and from the deeper layer of the prostate were removed separately. In four patients only the deep layer of the prostatic gland could be analysed.

After the kidney had been removed from the six patients undergoing nephrectomy, a wedge was excised from a part of the kidney macroscopically considered as normal. In one patient only cancerous tissue was found in the wedge. The fragment was divided into three parts consisting of the outer part of the cortex, the inner part of the cortex with the outer medulla, and the inner part of the medulla composed mainly of a pyramid (Figure 4). The prostatic and renal tissue specimens were carefully freed from blood and urine with a dry towel before storage in sterile tubes. All specimens collected were frozen at -20°C until they were analysed. The storage conditions were not found to influence the antibiotic concentrations detected.

Determination of Cefotaxime

Bioassay: Cefotaxime concentrations were determined by an agar well diffusion method using PDM-ASM agar, pH 7.2. The tests were made in plastic bioassay dishes, 24 cm $\times$ 24 cm (Nunc, Denmark), with an agar layer of approximately 4 mm. The test strain *Escherichia coli* ATCC 25992 was suspended in saline to 10^5 bacteria/ml and distributed over the plates. Excess suspension was sucked off immediately and the plates were dried for 60 min at 37°C . Wells 4 mm in diameter were punched out in the agar and filled to the brim with the specimens to be tested. The zone of inhibition was measured after 18 h at 37°C . Serum was tested undiluted or diluted 1:1 in normal pooled human serum. Urine was diluted in saline until the concentration was within the range of the assay. Tissue samples (approximately 200 mg) were thawed, weighed, minced with scissors and homogenized in an Ultra-Turrax homogenizer with 400 μl of phosphate buffered saline (PBS; 0.02 M phosphate buffer, pH 7.2 with 0.15 M NaCl) per sample. Fresh standard solutions of cefotaxime (range 0.3 to 40 $\mu\text{g}/\text{ml}$) were prepared for each test by diluting a fresh stock solution (1000 $\mu\text{g}/\text{ml}$ of active substance) in saline, serum, urine, prostatic and renal tissue homogenate. All samples were assayed in duplicate.

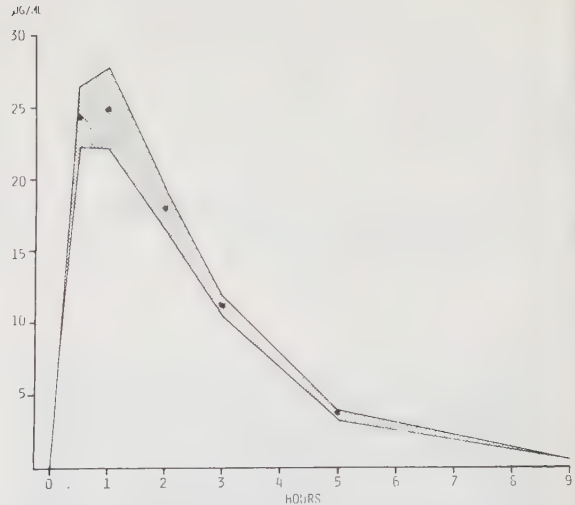


Figure 1: The standard serum curve for cefotaxime after injection of 1 g i.m. in a group of men (mean age 71, $n = 11$). The dots represent the mean values and the shadowed area the limits of the S.E.M.

The tissue was investigated for blood contamination (Dr. A. Grubb, Dept. of Clinical Chemistry, Malmö General Hospital) using a spectrophotometric method. It was found that blood contamination did not exceed 5% of the tissue weight.

Chemical assay: Cefotaxime concentrations in serum were determined using a high pressure liquid chromatographic (HPLC) method. 200 μl of internal standard (0.1 $\mu\text{g}/\text{ml}$ cefuroxime) and 3 ml of methanol were added to 1 ml of patient serum. After mixing, the sample was kept at room temperature for 15 min and then centrifuged for 10 min at 3,700 rpm. The supernatant was decanted and filtered through a Millipore filter. 20 μl of the filtrate were injected into a chromatograph (Waters Assoc.) equipped with a solvent delivery system model 6000 and an absorbance detector. Separation was performed on a Bondapak C_{18} column, and a mixture of acetic acid, water and methanol (1:72:27) was used as a mobile phase. Absorbance was measured at 254 nm.

The intra- and interassay variation of the method was tested on plasma samples containing 5 and 15 $\mu\text{g}/\text{ml}$ of cefotaxime. Variation was found to be about 2%.

All patient samples were analysed in duplicate.

Table 1: Concentration of cefotaxime in deep layer of prostatic gland*, serum* and prostate/serum ratio at various time intervals after i.m. injection of 1 g of cefotaxime.

	1-2 h	2-3 h	> 3 h
Prostatic gland	2.8	2.4	2.9
Serum	19.5	16.5	8.9
Prostate/serum ratio	15%	16%	31%
Number of specimens	7	5	3

* (mean, $\mu\text{g}/\text{g}$)

+ (mean, $\mu\text{g}/\text{ml}$)

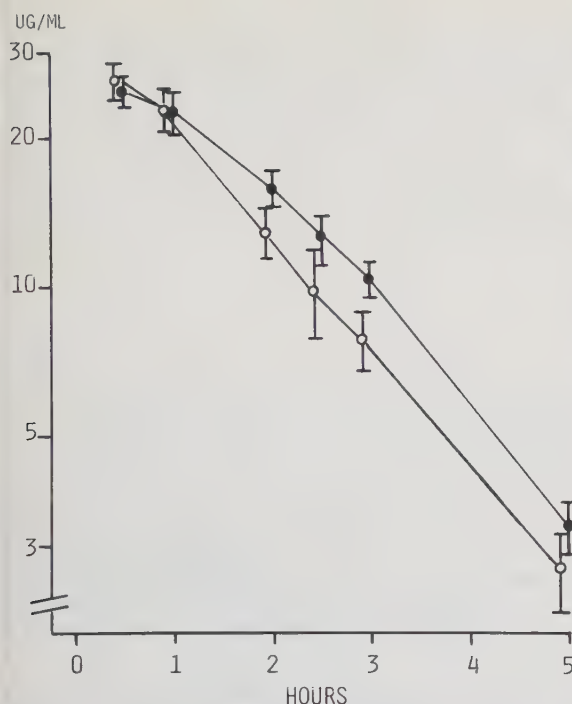


Figure 2: Serum elimination curve as determined by the biological method (●—●) and HPLC (○—○).

Results

Serum and Urine Concentrations of Cefotaxime

Serum: A standard serum concentration curve was obtained using serum samples taken at times indicated in the fixed schedule presented in Materials and Methods (Figure 1). There was a variation in peak serum concentrations ranging from 17.2 to 46 µg/ml. The mean serum peak (24.9 µg/ml) was found at 60 min. The half-life ($T_{1/2}$) was calculated to be 84 min.

In samples from seven patients analysed by two different methods (Figure 2) the mean serum peak found by the HPLC method was 26.1 µg/ml at 30 min, which is slightly higher than that obtained by the biological method (24.0 µg/ml). The half-life was 76 min.

Urine: In the four patients from whom urine samples were obtained, the mean concentrations at 2, 3, 5, and 24 h were 3,395 µg/ml, 3,107 µg/ml, 1,210 µg/ml, and 205 µg/ml, respectively. 50% of the administered dose was found to have been eliminated within the first three hours after injection, 66% after five hours and 87% after 24 hours.

Tissue Concentrations of Cefotaxime

Prostate: The concentrations of cefotaxime in both superficial and deep prostatic tissue were analysed in tissue

Table 2: Cefotaxime concentration in renal tissue ($\bar{x}$ = mean concentration, $n = 6$), range and kidney/serum ratio 145–195 min after 1 g of cefotaxime given intramuscularly. The tissue layers A, B and C are explained in Figure 4.

Tissue layer	$\bar{x}$ µg/g tissue	Range µg/g	Kidney/serum ratio
A	4.1	1.9–7.0	36%
B	4.2	1.9–10.8	33%
C	6.2	2.3–14.0	54%

samples from 12 of 16 patients. The average concentration of cefotaxime in superficial tissue was 3.9 µg/g tissue ($n = 12$), whereas in the deep prostatic tissue it was found to be 2.6 µg/g ($n = 16$). As the time between the injection of 1 g of cefotaxime and the resection of tissue varied (Figure 3), the samples were gathered in groups (Table 1). All tissue concentrations obtained from the prostate were lower than the serum samples taken simultaneously. The mean value between the first and second hour was 2.8 µg/g ($n = 7$), between the second and third hour 2.4 µg/g ($n = 5$) and 2.9 µg/g ($n = 3$) after the third hour. The ratio prostate/serum concentration of cefotaxime was calculated to be 15% within the second hour, 16% during the third, and 31% for the remaining three samples between the third and fifth hour.

Renal tissue: Figure 4 shows the wedge of renal tissue excised. The concentration of cefotaxime in renal tissue was found to vary considerably (Table 2). The time of sampling varied from 145–195 min after the cefotaxime injection. In the cortex and the middle part of the kidney (inner cortex and outer medulla) the mean values were identical –4.1 and 4.2 µg/g (range 1.9–7.0 µg/g and 1.9–10.8, respectively), amounting to 36% and 33% of the corresponding serum concentration. For the inner medulla the mean concentration was 6.2 µg/g (range 2.3–14.0) giving a renal tissue/serum ratio of 54%.

Side-effects during Cefotaxime Treatment

No side-effects were noted, nor were any drug-related abnormalities observed in any of the laboratory determinations.

Discussion

The standard serum concentration curve for cefotaxime was determined by the biological method since all other samples were analysed by this technique alone. In seven patients the serum concentration curves obtained from the biological and HPLC methods could be compared. The serum peaks were very close and were detected between 30 and 60 min after the injection. The slope of the curve obtained from the HPLC method was slightly steeper than that found with the biological method. This difference might be explained by the occurrence of a metabolite with some antibacterial activity. Such a metabolite has already been described (13, 14).

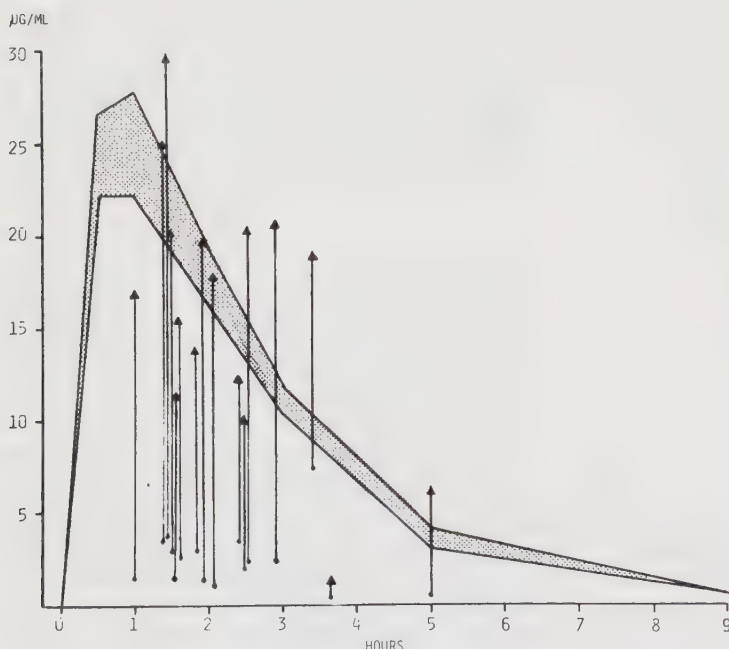


Figure 3: Concentration of cefotaxime in the deep prostatic gland tissue (●) and corresponding serum sample (▲) for 16 patients. A serum standard curve for cefotaxime is included as a frame of reference.

The standard serum concentration curve showed a half-life of 84 min. This curve can be considered representative for elderly men (mean age 71 years), an age group frequently encountered in urological wards. The results are comparable to those found for cefotaxime by other authors (15, 16) and are within the range of results found for cephalosporins in general (17).

The urine concentration of cefotaxime was found to be extremely high. With only a single i. m. injection of 1 g of cefotaxime daily, the urine concentration of the drug far exceeds, for nearly 24 hours, the MIC for most pathogens usually encountered in the urinary tract. The cumulative urinary excretion of cefotaxime was found to be comparable to that reported by other authors in the first hours after injection (16). About 85% was excreted within 24 hours.

Cefotaxime was found to penetrate the prostatic gland tissue. A slightly higher mean cefotaxime concentration was recorded in the superficial part of the prostate than in the deep specimen removed by transurethral resection. This may be explained by the fact that the superficial sample included urethral mucosa in addition to prostatic gland tissue. The mean values (Table 1) were found to decrease with a less pronounced slope than the corresponding serum curve, explaining the increasing prostate/serum ratio obtained from the samples taken in the second hour after the injection. The results are comparable to those observed in dogs (18).

In the renal tissue there appeared to be a difference between the cortex and the middle part of the paren-

chyma in comparison to the medulla, the latter being composed mainly of a pyramid. A relatively high concentration was found with a kidney/serum concentration ratio of 1:3 and 1:2. The relatively higher average concentration of cefotaxime in the medulla in comparison with the cortex might be explained by the abundance of collecting tubules in the former region, since cefotaxime, like most cephalosporins, is eliminated by renal excretion.

The concentration of the drug in tissues may be overestimated because of blood contamination. Thus the blood contamination of the tissues was investigated using a

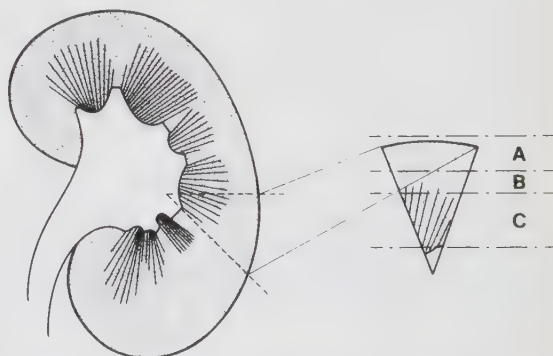


Figure 4: Schematic representation of a kidney and the wedge of parenchyma excised. The letters indicate the 3 different fragments analysed separately. The concentrations of cefotaxime in the tissues are given in Table 2.

spectrophotometric method. It was found that the blood contamination accounted for less than 5% of the total tissue weight. Taking the blood concentration into consideration, the values obtained for the prostate and the renal parenchyma still remain largely above the MIC recorded for the pathogens usually encountered in the urinary tract. The present results suggest that the distribution of cefotaxime in serum, urine, prostatic tissue and renal

parenchyma is adequate for the treatment of infections in the urinary tract.

Acknowledgement

Thanks are rendered to Dr. K. Bruch and Dr. R. Blomen from the medical division of Hoechst-Germany and Svenska Hoechst A. B. who kindly provided cefotaxime for the trial.

Literature

1. Hamilton-Miller, J. M. T., Brumfitt, W., Reynolds, A. V.: Cefotaxime (HR 756) a new cephalosporin with exceptional broad spectrum activity in vitro. *J. Antimicrob. Chemother.* 4 (1978) 437-444.
2. Heymès, R., Lutz, A., Schinner, E.: Experimental evaluation of HR 756, a new cephalosporin derivative: pre-clinical study. *Infection* 5 (1977) 259-260.
3. Bartmann, K., Tarbuc, R.: Untersuchungen zur Wirksamkeit von Cefotaxim gegen gramnegative Stäbchen *in vitro*. *Infection* 8, Suppl. 4 (1980) 372-384.
4. Besenthal, I., Ullmann, U.: Untersuchungen zur antibakteriellen Aktivität von Cefotaxim bei Beta-Laktamase-positiven und -negativen Bakterien. *Infection* 8, Suppl. 4 (1980) 359-364.
5. Chabbert, Y. A., Lutz, A. J.: HR 756, the syn isomer of a new methoxyimino cephalosporin with unusual antibacterial activity. *Antimicrob. Agents Chemother.* 14 (1978) 749-754.
6. Freitag, V., Friedrich, O., Kopf, P.-O., Wittmann, D. H.: Bakteriologische Prüfung von Cefotaxim, einem neuen halbsynthetischen Cephalosporin, im Rahmen der Routinediagnostik. *Infection* 8, Suppl. 4 (1980) 397-400.
7. Neuhaus, B.: Cefotaxim-Empfindlichkeit von *Pseudomonas aeruginosa* im Vergleich zu Aminoglykosiden, Alpha-Carboxypenicillin und Ureidopenicillinen. *Infection* 8, Suppl. 4 (1980) 430-432.
8. Neu, H. C., Aswapokee, N., Aswapokee, P., Fu, K. P.: HR 756, a new cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria. *Antimicrob. Agents Chemother.* 15 (1979) 273-281.
9. Fu, K. P., Neu, H. C.: Beta-lactamase stability of HR 756, a novel cephalosporin, compared to that of cefuroxime and cefoxitin. *Antimicrob. Agents Chemother.* 14 (1978) 322-326.
10. Grimm, H., Rangoonwala, R.: Bakteriologische In-vitro-Untersuchungen mit Cefotaxim im Vergleich zu Cefuroxim und Cefazolin. *Infection* 8, Suppl. 4 (1980) 385-387.
11. Malottke, R., Jentzen, A.: Vergleich der antibakteriellen Aktivität von Cephalotin, Cefazolin, Cefoxitin, Cefamandol, Cefuroxim und Cefotaxim. *Infection* 8, Suppl. 4 (1980) 401-407.
12. Sosna, J. P., Murray, P. R., Medoff, G.: Comparison of the *in vitro* activities of HR 756 with cephalothin, cefoxitin, and cefamandole. *Antimicrob. Agents Chemother.* 14 (1978) 876-879.
13. Chamberlain, J., Dell, D., Fromson, J., Coombes, J. D., MacDonald, C., McEwen, J.: Metabolism of cefotaxime in animals and man. International Symposium on Cefotaxime, Geneva (1980).
14. Reeves, D. S., White, L. O., Bahari, D., Bax, R. P., Holt, H. A.: Human metabolism of cefotaxime. International Symposium on Cefotaxime, Geneva (1980).
15. Fabricius, K.: Cefotaxim: Pharmakokinetische Daten bei sechs älteren Diabetikern mit Harnwegsinfekt. *Infection* 8, Suppl. 4 (1980) 484-486.
16. Lüthy, R., Münch, R., Blaser, J., Bhend, H., Siegenthaler, W.: Human pharmacology of cefotaxime (HR 756), a new cephalosporin. *Antimicrob. Agents Chemother.* 16 (1979) 127-133.
17. Andersson, K. E.: On the pharmacokinetics of cephalosporin antibiotics. *Scand. J. Infect. Dis., Suppl.* 13 (1978) 37-46.
18. Nielsen, O. S., Naber, K. G., Madsen, P. O.: Konzentrationen von Cefotaxim im Urogenitaltrakt: Experimentelle Studie beim Hund. *Infection* 8, Suppl. 4 (1980) 437-439.

